Phase 3 BEOVU® (brolucizumab-dbll) injection clinical trials in wet AMD

Beovu® (brolucizumab-dbll) Injection

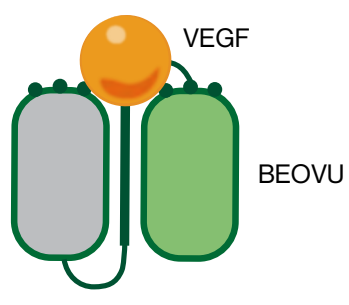
What is wet AMD?

Wet age-related macular degeneration (wet AMD) is a chronic, degenerative eye disease caused by an excess of VEGF, a protein that promotes the growth of abnormal blood vessels underneath the macula, the area of the retina responsible for sharp, central vision.[1,2] Fluid that leaks out of these abnormal blood vessels disrupts the normal retinal structure and ultimately damages the macula.[1,2]

What is BEOVU?

The BEOVU molecule binds to VEGF, preventing interaction with its receptors.[3,4] By inhibiting VEGF, BEOVU suppresses the growth of abnormal blood vessels and the potential for fluid leakage into the retina.[3,4]

Graphics are not drawn to scale.



INDICATIONS AND USAGE

BEOVU® (brolucizumab-dbll) injection is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

BEOVU is contraindicated in patients with ocular or periocular infections, active intraocular inflammation or known hypersensitivity to brolucizumab or any of the excipients in BEOVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

Please see additional Important Safety Information below.

HAWK and HARRIER

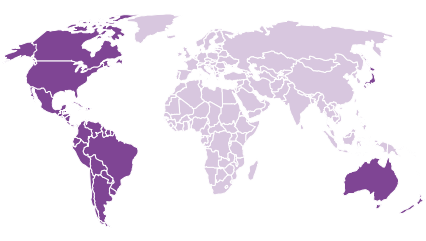
Study overview

The efficacy and safety of BEOVU were studied in patients with wet AMD in 2 pivotal Phase 3 clinical trials, HAWK and HARRIER.[5,6]

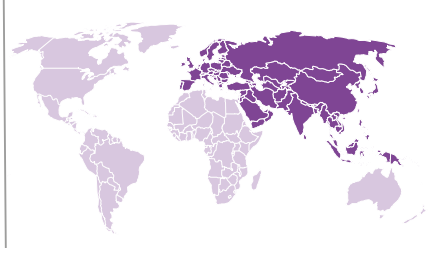
HAWK and HARRIER were global, randomized, double-masked Phase 3 clinical trials of 1459 adults with wet AMD carried out over 2 years.[5,6] Patients ranged in age from 50 to 97 (average, 76).[3]

The noninferiority trials compared the efficacy and safety of BEOVU with aflibercept for the treatment of wet AMD.[5,6]

HAWK
(NCT02307682)[5]
Study sites in the Americas, Israel, Australia, New Zealand, and Japan



HARRIER
(NCT02434328)[6]
Study sites across Europe and Asia



>1400[3] PATIENTS

730 BEOVU

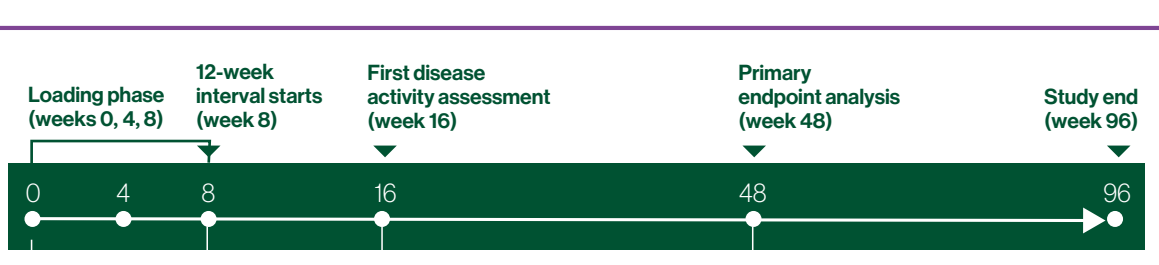
729 aflibercept

over **400** STUDY SITES

Following a loading phase*, wet AMD disease activity was assessed at scheduled visits over 96 weeks.[4] Visual acuity and anatomical parameters were measured, including retinal fluid and central subfield thickness *(see additional details below)*.[4]

Patients in the BEOVU arm were treated every 12 weeks following a loading phase* unless disease activity was noted.[3,4] BEOVU patients showing disease activity were adjusted to treatment every 8 weeks for the remainder of their participation in the study.[3,4] All aflibercept patients were treated every 8 weeks following the loading phase, according to the aflibercept label at the time of the study.[7]

* Treatment with BEOVU or aflibercept for wet AMD begins with 3 doses given at weeks 0, 4, and 8.



STUDY ENDPOINTS[5,6]

Primary Efficacy Endpoint

- Noninferiority in mean change in best corrected visual acuity (BCVA) from baseline to week 48

Secondary Endpoints

- Some secondary endpoints included the following:
  - number of patients on 3 month dosing interval at 48 weeks
  - change in central subfield thickness (CST) from baseline at week 16 and week 48
  - proportion of patients with intraretinal fluid (IRF) and/or subretinal fluid (SRF) at week 16 and week 48

How disease activity was measured: functional and anatomical parameters

BEST CORRECTED VISUAL ACUITY:

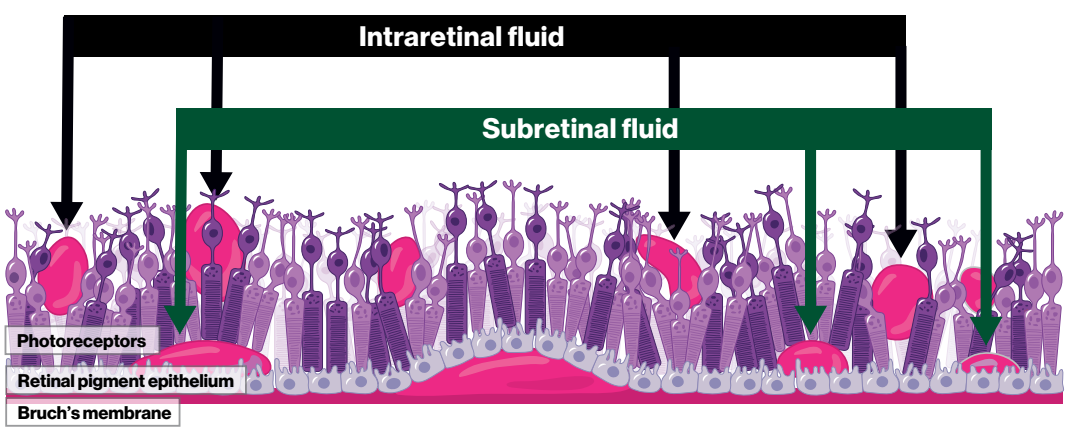
BCVA was used to compare a patient's vision at the start of the clinical trial with their vision at later visits.[3,4] BCVA was obtained using the standard and validated ETDRS eye chart.

CST:

Optical coherence tomography (OCT), an eye imaging method, was used to measure the thickness of the central subfield of the retina.[1] An increase in CST may indicate abnormal fluid accumulation.[1,8]

IRF AND/OR SRF:

OCT was also used to measure the presence of fluid in the retina. Fluid may be an indication of active blood vessel leakage, which may lead to damage to the retina.[1] Fluid within the retina is known as IRF, and fluid under the retina is known as SRF.[2]



IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with BEOVU, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering BEOVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection including with BEOVU. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the BEOVU clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms.

ADVERSE REACTIONS

Serious adverse reactions including endophthalmitis, retinal detachment, increases in intraocular pressure, and arterial thromboembolic events have occurred following intravitreal injections with BEOVU.

The most common adverse events (≥5% of patients) with BEOVU were vision blurred, cataract, conjunctival hemorrhage, vitreous floaters and eye pain.

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEOVU. Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEOVU. Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during dosing with BEOVU. The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEOVU is not known.

Please see full Prescribing Information here.

References

1. National Eye Institute. Facts About Age-Related Macular Degeneration. https://nei.nih.gov/health/maculardegen/armd_facts. Accessed September 9, 2019. **2.** Kim R. Introduction, mechanism of action and rationale for anti-vascular endothelial growth factor drugs in age-related macular degeneration. *Indian J Ophthalmol.* 2007;55(6):413-415. **3.** Beovu [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2019. **4.** Dugel P, 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]. *Ophthalmology.* doi:10.1016/j.ophtha.2019.04.017. **5.** ClinicalTrials.gov. Identifier NCT02307682. https://clinicaltrials.gov/ct2/show/NCT02307682. Accessed September 9, 2019. **6.** ClinicalTrials.gov. Identifier NCT02434328. https://clinicaltrials.gov/ct2/show/NCT02434328. Accessed September 9, 2019. **7.** Eylea [product information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2018. **8.** Kang SW, Park CY, Ham DI. The correlation between fluorescein angiographic and optical coherence tomographic features in clinically significant diabetic macular edema. *Am J Ophthalmol.* 2004;137(2):313-322.

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