HAWK and HARRIER: Phase III, Multicentre, Randomised, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration

Dugel PU *et al. Ophthalmology* 2020; 127:72–84.

Study design	Two similarly designed double-masked, multicentre, active-controlled, randomised Phase III trials (HAWK and HARRIER)
Patients	1,817 patients with untreated, active choroidal neovascularisation due to AMD
Inclusion criteria	≥50 years; active choroidal neovascularisation affecting central subfield; choroidal neovascularisation lesions secondary to AMD (including classic and occult) assessed by fluorescein angiography and comprising >50% of total lesion area; IRF and/or SRF affecting central subfield assessed on spectral-domain OCT; BCVA between 78 and 23 ETDRS letters; no fibrosis or geographic atrophy affecting central subfield
Exclusion criteria	Prior nAMD treatment at any time
Dosing	Intravitreal brolucizumab 3 mg* (HAWK only) or 6 mg or aflibercept 2 mg in study eye. 3 loading doses (Weeks 0, 4 and 8), followed by q12w/q8w brolucizumab; or q8w aflibercept
Duration	96 weeks
Endpoints	
Primary	Mean BCVA change from baseline to Week 48
Secondary	• Patients with IRF and/or SRF at Week 16 and Week 48 (%) • Changes in CST from baseline at Week 16 and Week 48 • Patients on q12w brolucizumab at Week 48 (%) • Presence of disease activity at Week 16 (%)
Results	
Functional	At Week 48, brolucizumab demonstrated non-inferiority to aflibercept in mean BCVA change from baseline in HAWK (p<0.001) and HARRIER (p<0.001)
Disease activity assessment & anatomical	• Significantly fewer brolucizumab treated eyes had IRF and/or SRF vs. aflibercept at Week 16 in HAWK (34% vs. 52%; p<0.001) and HARRIER (29% vs. 45%; p<0.001) and Week 48 in HAWK (31% vs. 45%; p<0.001) and HARRIER (26% vs. 44%; p<0.001) • At Week 16, after identical treatment exposure, fewer brolucizumab treated eyes had disease activity vs. aflibercept in HAWK (24.0% vs. 34.5%; p=0.001) and HARRIER (22.7% vs. 32.2%; p=0.002) • Greater CST reductions from baseline to Week 48 were observed with brolucizumab 6 mg vs. aflibercept in HAWK (LS mean -172.8 µm vs. -143.7 µm; p=0.001) and HARRIER (LS mean -193.8 µm vs. -143.9 µm; p<0.001)
Dosing interval	Over half of brolucizumab treated eyes were maintained on q12w dosing through Week 48 (56% [HAWK] and 51% [HARRIER])
Safety	Brolucizumab had an overall well-tolerated safety profile

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; LS, least squares; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; q8w, once every 8 weeks; q12w, once every 12 weeks; RPE, retinal pigment epithelium; SRF, subretinal fluid

*3 mg dose is not licensed in the UK

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Beovu brolucizumab

Prescribing Information:
▼Beovu® (Brolucizumab) 120 mg/ml solution for injection in pre-filled syringe

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC).

Presentation: Each pre-filled syringe contains 19.8 mg brolucizumab in 0.165 ml solution. I**ndication(s)**: Beovu is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD). **Dosage and administration**: Beovu must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose is 6mg brolucizumab (0.05 ml solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. The physician may further individualise treatment intervals based on disease activity. If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Beovu should be discontinued. **Elderly:** No dosage adjustment is required in patients aged 65 years or above. **Renal impairment:** No dosage adjustment is required in patients with renal impairment. **Hepatic impairment**: Beovu has not been studied in patients with hepatic impairment. No dosage adjustment is required in patients with hepatic impairment. **Paediatric population:** The safety and efficacy of Beovu in children and adolescents below 18 years of age have not been established. No data are available. Beovu is for intravitreal use only. The pre-filled syringe is for single use only. Each pre-filled syringe should only be used for the treatment of a single eye. Since the volume contained in the pre-filled syringe (0.165 ml) is greater than the recommended dose (0.05 ml), a portion of the volume contained in the pre-filled syringe must be discarded prior to administration. Injecting the entire volume of the pre-filled syringe could result in overdose. To expel the air bubble along with excess medicinal product, the plunger should be slowly depressed until the edge below the dome of the rubber stopper is aligned with the 0.05 ml dose mark (equivalent to 50 µl, i.e. 6 mg brolucizumab). **Contraindications**: Hypersensitivity to the active substance or to any of the excipients. Patients with active or suspected ocular or periocular infections. Patients with active intraocular inflammation. **Warnings/Precautions**: Intravitreal injections, including those with Beovu, have been associated with endophthalmitis, intraocular inflammation, traumatic cataract and retinal detachment. Retinal artery occlusion has been reported with the use of Beovu. Proper aseptic injection techniques must always be used when administering Beovu. Patients should be instructed to report any symptoms suggestive of the above-mentioned events without delay. Transient increases in intraocular pressure have been seen within 30 minutes of intravitreal injection with vascular endothelial growth factor (VEGF) inhibitors, including Beovu. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Beovu while the intraocular pressure is ≥30 mmHg). Both intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. The safety and efficacy of Beovu administered in both eyes concurrently have not been studied. As this is a therapeutic protein, there is a potential for immunogenicity with Beovu. Patients should be instructed to inform their physician if they develop symptoms such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light. There are no data available on the concomitant use of Beovu with other anti-VEGF medicinal products in the same eye. Beovu should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular). In intravitreal anti-VEGF treatments, the dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of: a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity; a retinal break; a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50% of the total lesion area; performed or planned intraocular surgery within the previous or next 28 days. Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD include a large and/or high pigment epithelial retinal detachment. When initiating Beovu therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears. Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. Systemic adverse events, including non-ocular haemorrhages and arterial thromboembolic events, have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with AMD with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 3 months. Caution should be exercised when treating such patients. This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”. **Interactions**: No interaction studies have been performed. **Fertility, pregnancy and lactation**: Women of childbearing potential should use effective contraception during treatment with Beovu and for at least one month after the last dose when stopping treatment with Beovu. There are no or limited amount of data from the use of Beovu in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Although the systemic exposure after ocular administration is very low, Beovu should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. It is unknown whether Beovu is excreted in human milk. A risk to the breast-fed newborn/infant cannot be excluded. Beovu is not recommended during breast-feeding and breast-feeding should not be started for at least one month after the last dose when stopping treatment with Beovu. A decision must be made whether to discontinue breast-feeding or to abstain from Beovu therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No reproductive or fertility studies have been conducted. VEGF inhibition has been shown to affect follicular development, corpus luteum function and fertility. Based on the mechanism of action of VEGF inhibitors, there is a potential risk for female reproduction, and to embryofoetal development. **Driving and using machines:** Beovu has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances following the intravitreal injection and the associated eye examination. Patients should not drive or use machines until visual function has recovered sufficiently. **Undesirable effects:** The most serious adverse reactions were blindness, endophthalmitis, retinal artery occlusion and retinal detachment. **Common (≥1/100 to <1/10):**Hypersensitivity (including urticaria, rash, pruritus, erythema), reduced visual acuity, retinal haemorrhage, uveitis, iritis, vitreous detachment, retinal tear, cataract, conjunctival haemorrhage, vitreous floaters, eye pain, intraocular pressure increase, conjunctivitis, retinal pigment epithelial tear, vision blurred, corneal abrasion, punctate keratitis. **Uncommon (≥1/1,000 to <1/100):** blindness, endophthalmitis, retinal artery occlusion, retinal detachment, conjunctival hyperaemia, increased lacrimation, abnormal sensation in eye, detachment of retinal pigment epithelium, vitritis, anterior chamber inflammation, iridocyclitis, anterior chamber flare, corneal oedema, vitreous haemorrhage. **Other Adverse Effects:** Please consult the Summary of Product Characteristics for a detailed listing of all adverse events before prescribing. **Legal classification:** POM. **Marketing Authorisation (MA) number, quantities and price:** EU/1/19/1417/001 – single dose pre-filled syringe pack £816 **Date of last revision of prescribing information**: February 2020 **Full Prescribing Information available from**: Novartis Pharmaceuticals UK Limited, 2nd Floor, The Westworks Building, White City Place, 195 Wood Lane, London, W12 7FQ. UNITED KINGDOM. Tel: 01276 692255.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.UK/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the patient safety information (PSI) tool at https://psi.novartis.com

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Additional Safety Information

Following post-marketing reports, Novartis has confirmed a safety signal of adverse events of “retinal vasculitis” and/or “retinal vascular occlusion” that may result in severe vision loss. Typically these events occurred in the presence of intraocular inflammation. We are in discussion with regulatory authorities to update our SmPC. Please contact Medical Information for more details

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