▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – BEOVU® (BROLUCIZUMAB) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Brolucizumab (*rbe*)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL solution for injection contains 120 mg of brolucizumab*.

*Brolucizumab is a humanised monoclonal single-chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa, produced in *Escherichia coli* cells by recombinant DNA technology.

Beovu 120 mg/mL solution for injection in pre-filled syringe

Each pre-filled syringe contains 19.8 mg brolucizumab in 0.165 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL containing 6 mg of brolucizumab.

Beovu 120 mg/mL solution for injection in vial

Each vial contains 27.6 mg brolucizumab in 0.23 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL containing 6 mg of brolucizumab.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Solution for injection.

Sterile, clear to slightly opalescent, colourless to slightly brownish-yellow and preservative-free aqueous solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Beovu is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).

4.2 DOSE AND METHOD OF ADMINISTRATION

Beovu must be administered by a qualified ophthalmologist experienced in administering intravitreal injections.

Dosage

The recommended dose is 6 mg 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 with disease activity, treatment every 8 weeks (2 months) should be considered. In patients without disease activity, treatment up to every 12 weeks (3 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.

Special populations

Hepatic impairment

No dosage regimen adjustment is required in patients with hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Renal impairment

No dosage regimen adjustment is required in patients with renal impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Elderly patients (aged 65 years and over)

No dose adjustment is required in patients aged 65 years or above (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric patients (below 18 years)

The safety and efficacy of Beovu in children and adolescents below 18 years of age have not been established.

Method of administration

Beovu is for intravitreal use only.

As with all medicinal products for intravitreal use, the solution should be inspected visually upon removal from the refrigerator and prior to administration. If particulates or cloudiness are visible, Beovu must not be used and appropriate replacement procedures followed.

Do not use if the packaging, or its content is damaged or expired. Detailed instructions for use are provided in the pack in the 'How to Use' leaflet.

The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see Section 4.3 CONTRAINDICATIONS). Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 mL is then delivered slowly; a different scleral site should be used for subsequent injections.

The safety and efficacy of Beovu administered in both eyes concurrently have not been studied.

Pre-filled syringe

The pre-filled syringe is for single use only. Each pre-filled syringe should only be used for the treatment of a single eye. Discard any residue.

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 in 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).

Vial

The vial is for single use only. Each vial should only be used for the treatment of a single eye. Discard any residue.

Since the volume contained in the vial (0.23 mL) is greater than the recommended dose (0.05 mL), a portion of the volume contained in the vial must be discarded prior to administration.

Injecting the entire volume in the vial could result in overdose. To expel the air bubble along with excess medicinal product, the air should be carefully expelled from the syringe and the dose adjusted to the 0.05 mL mark (equivalent to 50 µL, i.e. 6 mg brolucizumab).

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 LIST OF EXCIPIENTS).
- Patients with active or suspected ocular or periocular infections.
- Patients with active intraocular inflammation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Intravitreal injection-related reactions

Intravitreal injections, including those with Beovu, have been associated with endophthalmitis, intraocular inflammation, and retinal detachment (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 injection, similar to those observed with intravitreal administration of other VEGF inhibitors (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Sustained intraocular pressure increases have also been reported with Beovu. Both intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. Special precaution is needed in patients with poorly controlled glaucoma.

Arterial thromboembolic events

There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors. ATEs include for example ischaemic stroke or myocardial infarction.

Bilateral treatment

The safety and efficacy of brolucizumab administered in both eyes concurrently have not been studied.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with brolucizumab (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Concomitant use of other anti-VEGF

There are no data available on the concomitant use of Beovu with other anti-VEGF medicinal products in the same eye. Brolucizumab should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular).

Withholding treatment

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.

Retinal pigment epithelial tear

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 brolucizumab therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Rhegmatogenous retinal detachment or macular holes

Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.

Systemic effects following intravitreal use

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.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal interaction studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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 reproduction, and to embryofetal development.

Use in pregnancy – Pregnancy Category D

There are no adequate and well-controlled studies of Beovu administration in pregnant women and no animal reproduction studies have been conducted. The potential risk of use of Beovu in pregnancy is unknown. However, based on the anti-VEGF mechanism of action, brolucizumab must be regarded as potentially teratogenic and embryo/fetotoxic. Therefore, brolucizumab should not be used during pregnancy unless the expected benefit outweighs the potential risks to the fetus.

Use in lactation

It is unknown whether brolucizumab is excreted in human milk. There are no data on the effects of brolucizumab on the breast-fed newborn/infant or on milk production. Because of the potential for adverse drug reactions in the breast-fed newborn/infant, breast-feeding is not recommended during treatment and for at least one month after the last dose when stopping treatment with Beovu.

Women of childbearing potential/contraception in females

Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with Beovu and for at least one month after the last dose when stopping treatment with Beovu.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients may experience temporary visual disturbances after an intravitreal injection with Beovu and the associated eye examination (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) and should therefore be advised not to drive or use machinery until visual function has recovered sufficiently.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

A total of 1,088 patients treated with Beovu constituted the safety population in the two Phase III studies HAWK and HARRIER with a cumulative 96 weeks' exposure to Beovu and 730 patients treated with the recommended dose of 6 mg (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

The most frequently reported adverse drug reactions (in >5% of patients treated with Beovu) 6 mg were reduced visual acuity (7.3%), cataract (7.0%), conjunctival haemorrhage (6.3%) and vitreous floaters (5.1%).

Serious adverse drug reactions reported in <1% of the patients treated with Beovu 6 mg were endophthalmitis, uveitis, blindness, retinal artery occlusion and retinal detachment.

Tabulated list of adverse reactions

Adverse reactions from clinical studies (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

Adverse drug reactions	Beovu (N=730)	Aflibercept (N=729)	Frequency category
Eye disorders			
Visual acuity reduced	7.3	7.5	Common
Retinal haemorrhage	4.1	3.2	Common
Uveitis	1.6	0.1	Common
Iritis	1.2	0.3	Common
Vitreous detachment	4.0	3.3	Common
Retinal tear	1.2	0.7	Common
Cataract	7.0	11.1	Common
Conjunctival haemorrhage	6.3	7.0	Common
Vitreous floaters	5.1	2.9	Common
Eye pain	4.9	6.2	Common
Intraocular pressure increase	3.8	4.5	Common
Conjunctivitis	3.3	1.6	Common
Retinal pigment epithelial tear	2.7	1.1	Common
Vision blurred	1.9	1.6	Common
Corneal abrasion	1.5	2.2	Common
Punctate keratitis	1.4	2.3	Common
Endophthalmitis	0.7	0.1	Uncommon
Blindness	0.8	0.3	Uncommon

Adverse drug reactions	Beovu (N=730)	Aflibercept (N=729)	Frequency category
Retinal artery occlusion	0.8	0.1	Uncommon
Retinal detachment	0.7	0.4	Uncommon
Conjunctival hyperaemia	1.0	1.1	Uncommon
Lacrimation increased	1.0	1.1	Uncommon
Abnormal sensation in eye	0.8	1.8	Uncommon
Detachment of retinal pigment epithelium	0.5	0.4	Uncommon
Vitritis	0.4	0.4	Uncommon
Anterior chamber inflammation	0.4	0	Uncommon
Iridocyclitis	0.4	0.1	Uncommon
Anterior chamber flare	0.3	0	Uncommon
Corneal oedema	0.3	0	Uncommon
Vitreous haemorrhage	0.1	0.4	Uncommon
Immune system disorders			
Hypersensitivity[a)]	1.8	1.4	Common

[a)] *Including urticaria, rash, pruritus, erythema*

Arterial thromboembolic events

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms.

Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with Beovu. The immunogenicity of Beovu was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Beovu in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Beovu with the incidence of antibodies to other products may be misleading.

The pre-treatment incidence of anti-brolucizumab antibodies was 35 – 52%. After dosing with Beovu for 88 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 23 – 25% of patients.

Among patients with treatment-emergent antibodies, a higher number of intraocular inflammation events were observed. The significance of anti-brolucizumab antibodies on clinical efficacy and safety of Beovu is not known.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosing with greater than recommended injection volume may increase intraocular pressure. In the event of overdose, intraocular pressure should therefore be monitored and, if deemed necessary by the treating physician, appropriate treatment should be initiated.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Ophthalmologicals, antineovascularisation agents, ATC code: S01LA06

Mechanism of action

Increased levels of signalling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathological ocular angiogenesis and retinal oedema in age-related macular degeneration. Brolucizumab binds with picomolar affinity to VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$, and $VEGF_{165}$), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A binding to its receptors, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability.

Pharmacodynamic effects

Neovascular (wet) age-related macular degeneration (AMD) is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal thickening or oedema and/or intraretinal/subretinal haemorrhage, resulting in loss of visual acuity.

In the HAWK and HARRIER studies, related anatomical parameters were part of the disease activity assessments guiding treatment decisions. Reductions in central subfield thickness (CST) and in presence of intraretinal/subretinal fluid (IRF/SRF) or sub-retinal pigment epithelium (sub-RPE) fluid (pre-specified secondary endpoints) were observed in patients treated with Beovu as early as 4 weeks after treatment initiation and up to Week 48 and Week 96. Statistically significant greater reductions in CST and in presence of IRF/SRF relative to aflibercept were demonstrated at Weeks 16 and 48.

In these studies, for patients treated with Beovu, reductions in CNV lesion size were observed as early as 12 weeks, and at Weeks 48 and 96 after treatment initiation.

At week 16, the reduction in CST on Beovu was statistically significantly superior versus aflibercept in both studies (HAWK: -161 vs. -134 microns, $p=0.0008$; HARRIER: -174 vs. -134 microns, $p<0.0001$). This decrease from baseline in CST was also statistically significant at week 48 (HAWK: -173 vs. -144 microns, $p=0.0012$; HARRIER: -194 vs. -144 microns, $p<0.0001$), and maintained to the end of each

study at week 96 (HAWK: -175 vs. -149 microns, p=0.0115; HARRIER: -198 vs. -155 microns, p<0.0001).

At week 16, the percentage of patients with IRF and/or SRF fluid was statistically significantly lower on Beovu versus aflibercept in both studies (HAWK: 34% vs.52%, p<0.0001; HARRIER: 29% vs. 45%, p<0.0001). This difference was also statistically significant at week 48 (HAWK: 31% vs. 45%, p=0.0001; HARRIER: 26% vs. 44%, p<0.0001), and maintained to the end of each study at week 96 (HAWK: 24% vs. 37%, p=0.0002; HARRIER: 24% vs. 39%, p<0.0001).

At week 16, the percentage of patients with sub-RPE fluid was statistically significantly lower on Beovu versus aflibercept in both studies (HAWK: 19% vs.27%, p=0.0030; HARRIER: 16% vs. 24%, p=0.0041). This difference was also statistically significant at week 48 (HAWK: 14% vs. 22%, p=0.0035; HARRIER: 13% vs. 22%, p=0.0007), and maintained to the end of each study at week 96 (HAWK: 11% vs. 15%, p=0.1213; HARRIER: 17% vs. 22%, p=0.0371).

Clinical trials

The efficacy and safety of Beovu were assessed in two randomised, multicentre, double-masked, active-controlled Phase III studies (HAWK and HARRIER) in patients with neovascular (wet) AMD. A total of 1,817 patients were treated in these studies for two years (1,088 on BEOVU and 729 on aflibercept). Patient ages ranged from 50 to 97 years, with a mean age of 76 years.

In HAWK, patients were randomised in a 1:1:1 ratio to the following dosing regimens:

- Beovu 3 mg administered every 12 or 8 weeks after the first 3 monthly doses;
- Beovu 6 mg administered every 12 or 8 weeks after the first 3 monthly doses;
- aflibercept 2 mg administered every 8 weeks after the first 3 monthly doses.

In HARRIER, patients were randomised in a 1:1 ratio to the following dosing regimens:

- Beovu 6 mg administered every 12 or 8 weeks after the first 3 monthly doses;
- aflibercept 2 mg administered every 8 weeks after the first 3 monthly doses.

In both studies, after the first three monthly doses (weeks 0, 4 and 8), brolucizumab patients were treated every 12 weeks, with the option of adjusting to a dosing interval every 8 weeks based on disease activity. Disease activity was assessed by a physician during the first 12-week interval (at weeks 16 and 20) and at each subsequent scheduled 12-weekly treatment visit. Patients who showed disease activity (e.g. decreased visual acuity, increased CST and/or presence of IRF/SRF or sub-RPE fluid) at any of these visits were adjusted to an 8-weekly treatment interval.

The below criteria for disease activity were provided as guidance and the Investigator should have considered the guidance while also applying their own expert judgment when making q12w/q8w treatment decisions.

Disease activity guidance criteria at Week 16:

- Decrease in BCVA of ≥ 5 letters compared with Baseline
- Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75 µm compared with Week 12
- Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 12

- New or worse IRF/intraretinal cysts compared with Week 12

Disease activity guidance criterion at Weeks 20, 32, and 44:

- Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 12

Disease activity guidance criterion at Weeks 56, 68, 80, and 92:

- Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 48

Results

The primary efficacy endpoint for the studies was the change from baseline in Best Corrected Visual Acuity (BCVA) to week 48, as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, with the primary objective being to demonstrate non-inferiority of Beovu versus aflibercept. In both studies, Beovu (administered in an every 12 weeks or an every 8 weeks regimen) demonstrated non-inferior efficacy to aflibercept 2 mg (administered every 8 weeks). The visual acuity gains observed in the first year were maintained in the second year.

Detailed results of both studies are shown in Tables 2 and 3 and in Figure 1 below.

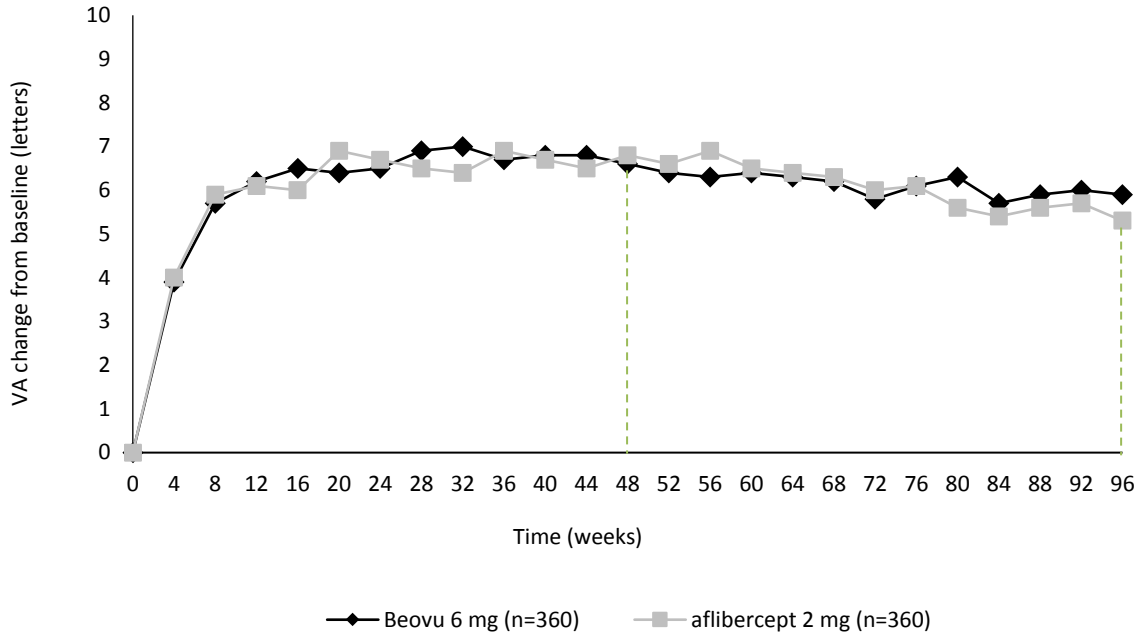
Table 2 Visual acuity outcomes at weeks 48 and 96 in Phase III - HAWK and HARRIER studies

		HAWK			HARRIER		
Efficacy outcome	**Week**	**Beovu 6 mg (n=360)**	**Aflibercept 2 mg (n=360)**	**Difference (95% CI) brolucizumab – aflibercept**	**Beovu 6 mg (n=370)**	**Aflibercept 2 mg (n=369)**	**Difference (95% CI) brolucizumab – aflibercept**
Mean BCVA at Baseline	-	60.8 (SD=13.7)	60.0 (SD=13.9)	-	61.5 (SD=12.6)	60.8 (SD=12.9)	-
Mean change from baseline in BCVA (measured by ETDRS letters score)	48	6.6 (SE=0.71)	6.8 (SE=0.71)	-0.2 (-2.1, 1.8) P<0.0001 [a)]	6.9 (SE=0.61)	7.6 (SE=0.61)	-0.7 (-2.4, 1.0) P <0.0001 [a)]
	36 – 48 [b)]	6.7 (SE=0.68)	6.7 (SE=0.68)	0.0 (-1.9, 1.9) P<0.0001 [a)]	6.5 (SE=0.58)	7.7 (SE=0.58)	-1.2 (-2.8, 0.4) P=0.0003 [a)]
	96	5.9 (SE=0.78)	5.3 (SE=0.78)	0.5 (-1.6, 2.7)	6.1 (SE=0.73)	6.6 (SE=0.73)	-0.4 (-2.5,1.6)
% of patients who gained at least 15 letters of vision	48	33.6	25.4	8.2 (2.2, 15.0)	29.3	29.9	-0.6 (-7.1, 5.8)
	96	34.2	27.0	7.2 (1.4, 13.8)	29.1	31.5	-2.4 (-8.8, 4.1)
% of patients who lost visual acuity (%) (≥15 letters of BCVA loss)	48	6.4	5.5	0.9 (-2.7, 4.3)	3.8	4.8	-1.0 (-3.9, 2.2)
	96	8.1	7.4	0.7 (-3.6, 4.6)	7.1	7.5	-0.4 (-3.8, 3.3)

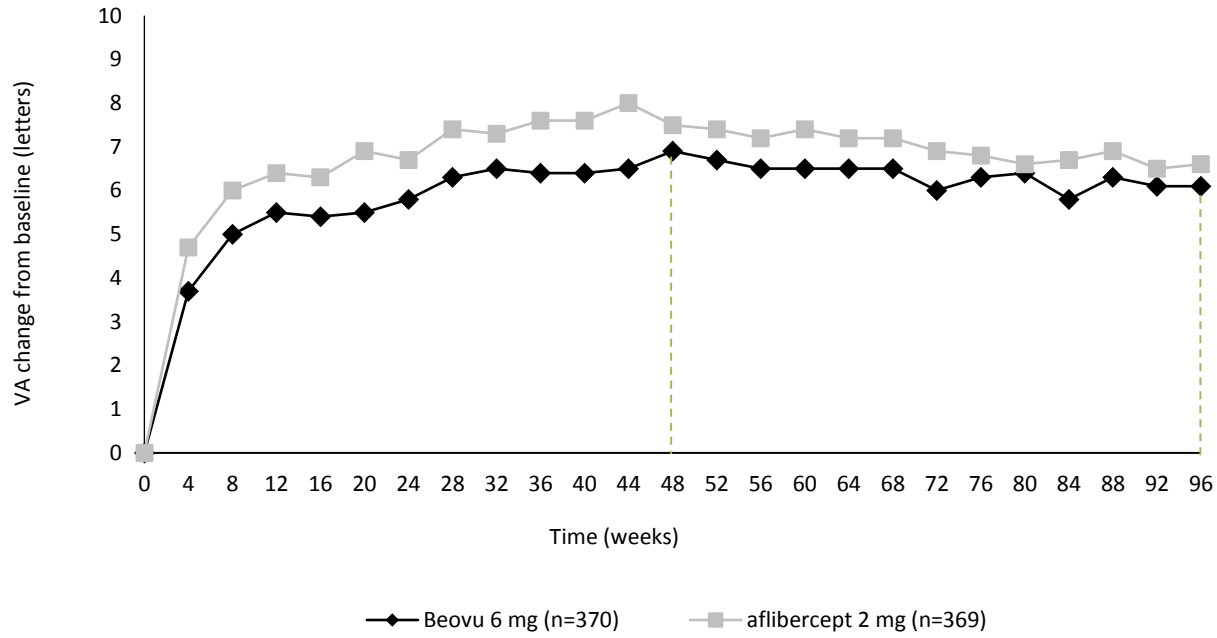
BCVA: Best Corrected Visual Acuity; missing data are imputed using last observation carried forward (LOCF) method
ETDRS: Early Treatment Diabetic Retinopathy Study
[a)] P-value referring to the non-inferiority hypothesis with a non-interiority margin of 4.0 letters
[b)] Key secondary endpoint, accounting for differences in timing of Beovu and aflibercept treatments

Figure 1 **Mean change in visual acuity from baseline to week 96 in HAWK and HARRIER studies**

HAWK



HARRIER



These visual acuity gains were achieved with 56% and 51% of patients treated with Beovu 6 mg on a 12-weekly dosing interval at week 48, and with 45% and 39% of patients at week 96 in HAWK and HARRIER, respectively. Among patients identified as eligible for the 12-weekly regimen during the first 12-week interval, 85% and 82% remained on the 12-weekly dosing interval up to week 48. Of

patients on the 12-weekly interval at week 48, 82% and 75% remained on the 12-weekly dosing interval up to week 96.

Treatment effects in evaluable subgroups (e.g. age, gender, race, baseline visual acuity, baseline retinal thickness, lesion type, lesion size, fluid status) in each study were generally consistent with the results in the overall populations.

Disease activity was assessed by changes in visual acuity and/or anatomical parameters, including CST and/or presence of IRF/SRF or sub-RPE. At week 16, when disease activity was first assessed for determining the treatment interval, statistically fewer patients showed disease activity on Beovu 6 mg compared to aflibercept 2 mg (24% vs 35% in HAWK, p=0.0013; 23% vs 32% in HARRIER, p=0.0021). Disease activity was assessed throughout the studies. Anatomical parameters of disease activity were decreased at week 48 and at week 96 for Beovu compared to aflibercept.

In both studies, Beovu demonstrated clinically meaningful increases from baseline in the pre-specified secondary efficacy endpoint of patient-reported outcomes, reported through the National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in BCVA. Patient-reported outcome benefits were maintained in the second year.

No clinically meaningful differences were found between Beovu and aflibercept in changes from baseline to week 48 in NEI VFQ-25 total score and subscales (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, colour vision and peripheral vision).

Paediatric population

The safety and efficacy of Beovu in children and adolescents below 18 years of age have not been established (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Paediatric patients (below 18 years) for information on paediatric use).

5.2 PHARMACOKINETIC PROPERTIES

Beovu is administered directly into the vitreous to exert local effects in the eye.

Absorption/Distribution

After intravitreal administration of 6 mg brolucizumab per eye to patients with nAMD, the mean C_{max} of free brolucizumab in the plasma was 49.0 ng/mL (range: 8.97 to 548 ng/mL) and was attained in 1 day.

Excretion

Brolucizumab is a monoclonal antibody fragment and no drug metabolism studies have been conducted. As a single-chain antibody fragment, free brolucizumab is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF, passive renal elimination and metabolism via proteolysis.

After intravitreal injections, brolucizumab was eliminated with an apparent systemic half-life of 4.4 days. Concentrations were generally near or below the quantitation limit (<0.5 ng/mL) approximately 4 weeks after dosing in most patients. Beovu did not accumulate in the serum when administered intravitreally every 4 weeks.

Special populations

Elderly (aged 65 years and over)

In the HAWK and HARRIER clinical studies, approximately 90% (978/1,088) of patients randomised to treatment with Beovu were ≥65 years of age and approximately 60% (648/1,088) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

Race/Ethnicity

There were no ethnic differences in systemic pharmacokinetics following intravitreal injection in a study with 24 Caucasian and 26 Japanese patients.

Renal impairment

Mild to severe renal impairment should have no impact on the overall systemic exposure to brolucizumab, because the systemic concentration of brolucizumab is driven by the distribution from the eye rather than the elimination rate and because the systemic exposure of free brolucizumab is low.

The systemic clearance of brolucizumab was evaluated in nAMD patients who had both serum brolucizumab pharmacokinetic and creatinine clearance data available. Subjects with mild (50-79 mL/min [n=13]) renal impairment had mean systemic clearance rates of brolucizumab which were within 15% of the mean clearance rate for subjects with normal renal function (≥80 mL/min [n=25]). Patients with moderate (30-49 mL/min [n=3]) renal impairment had mean systemic clearance rates of brolucizumab which were lower than patients with normal renal function but the number of patients was too low to make definitive conclusions. No patients with severe (<30 mL/min) renal impairment were studied.

Hepatic impairment

Brolucizumab has not been studied in patients with hepatic impairment. Mild to severe hepatic impairment should have no impact on the overall systemic exposure to brolucizumab, because metabolism occurs via proteolysis and does not depend on hepatic function.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted on the mutagenic or clastogenic potential of brolucizumab. Considering the monoclonal antibody nature, brolucizumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No studies have been conducted on the carcinogenic potential of brolucizumab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium citrate, sucrose, polysorbate 80 and water for injections.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Pre-filled syringe

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Prior to use, the unopened blister may be kept at room temperature (25°C) for up to 24 hours.

Keep the pre-filled syringe in its sealed blister and in the outer carton in order to protect from light.

Refer to pre-filled syringe for expiry date.

Beovu must be kept out of the reach and sight of children.

Vial

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Prior to use, the unopened vial may be kept at room temperature (25°C) for up to 24 hours.

Keep the vial in the outer carton in order to protect from light.

Refer to vial for expiry date.

Beovu must be kept out of the reach and sight of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Pre-filled syringe

0.165 mL sterile solution in a pre-filled syringe consisting of a 0.5 mL long clear, colourless Type 1 glass syringe, rubber plunger stopper, an OVS tamper-evident closure system containing a rubber tip

cap and a purple finger grip. The external surface of the pre-filled syringe is sterile and it is packed in a transparent rigid blister.

Pack size of 1 pre-filled syringe.

Vial

0.230 mL sterile solution in a clear Type 1 glass vial with a coated rubber stopper sealed with an aluminium cap with a purple plastic flip-off disk.

Pack size of 1 vial and 1 blunt filter needle (18G x 1½", 1.2 mm x 40 mm, 5 µm) in a soft blister.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Brolucizumab is a humanized monoclonal single-chain Fv (scFv) antibody fragment.

CAS number

1531589-13-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16 January 2020

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

Internal document code: beo150120i based on CDS dated 11-Jan-2019