▼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 0.230 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),
- Diabetic macular oedema (DME).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dosage

Wet AMD

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.

Following the first three loading doses, the interval between two doses should not be less than every 8 weeks (2 months) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Diabetic Macular Oedema (DME)

The recommended dose is 6 mg brolucizumab (0.05 mL solution) administered by intravitreal injection every 6 weeks for the first 5 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. 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. After 12 months of treatment, in patients without disease activity, treatment intervals up to 16 weeks (4 months) could be considered.

Following the first five loading doses, the interval between 2 doses should not be less than every 8 weeks (2 months) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 (0.230 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

Endophthalmitis, intraocular inflammation and retinal detachments

Intravitreal injections, including those with Beovu, have been associated with endophthalmitis, intraocular inflammation, and retinal detachments (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 endophthalmitis, intraocular inflammation or retinal detachment without delay and should be managed appropriately (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

In a Phase IIIa clinical study (MERLIN), patients with nAMD who received Beovu every 4 weeks maintenance dosing experienced a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion than patients who received Beovu every 8 or 12 week maintenance dosing in the pivotal phase III Clinical studies (HAWK and HARRIER) (see Section 4.8 ADVERSE EFFECTS). The interval between two Beovu doses during maintenance treatment should not be less than 8 weeks (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Retinal vasculitis and/or retinal vascular occlusion

Retinal vasculitis and/or retinal vascular occlusion have been reported with the use of Beovu. These immune mediated adverse events may occur following the first intravitreal injection. Discontinue treatment with Beovu in patients who develop these events. Patients treated with Beovu who experience intraocular inflammation may be at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored. Concomitant intraocular inflammation was reported, but not in all cases (see Section 4.3 CONTRAINDICATIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Prior treatment was not reported for all cases but some patients had previous intravitreal VEGF inhibitor therapy. Patients should be monitored and instructed to report any change in vision without delay.

Intraocular pressure increases

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. However, 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. The potential risk of use of Beovu in pregnancy is unknown.

In an enhanced pre- and postnatal development (ePPND) study, in pregnant cynomolgus monkeys, brolucizumab was administered to animals by intravitreal (IVT) injection to one eye at doses up to 6 mg once every 4 weeks until delivery. One additional injection was administered to a subset of animals 28 days post-partum. There was no effect on embryofetal development, pregnancy or parturition; or on the survival, growth, or postnatal development of offspring. This represents an exposure approximately 6-times the human exposure (based on serum C_{max}) at the proposed clinical dose of 6mg. 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. In an ePPND study, brolucizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys. 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

Females 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

Wet AMD population

A total of 1,088 patients treated with brolucizumab 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.

DME population

The safety of Beovu was studied in two, Phase III active controlled studies (KESTREL and KITE) conducted respectively in 368 patients with visual impairment due to DME treated with the recommended dose of brolucizumab 6 mg for 100 weeks.

The ocular and non-ocular events in the KESTREL and KITE studies were reported with a frequency and severity similar to those seen in the wet AMD trials. Retinal vascular occlusion was reported in four patients (1.1%) treated with Beovu and two patients (0.5%) treated with aflibercept 2 mg. Retinal vasculitis was reported in one patient (0.3%) treated with Beovu and no patients treated with aflibercept 2 mg. The adverse drug reactions of iridocyclitis and vitreous haemorrhage were observed at a higher frequency (category of common) in the pooled DME Phase III studies as compared to the pooled nAMD Phase III studies (category of uncommon). In addition, the adverse drug reaction retinal vascular occlusion was observed at a frequency category of common in the pooled DME Phase III studies.

Tabulated list of adverse reactions

The adverse reactions experienced following administration of Beovu in clinical studies are summarised in Table 1 below.

Adverse reactions (Table 1) are listed according to the MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Frequency categories for each adverse reaction are based on the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Frequencies of adverse reactions in clinical studies

MedDRA System organ class	Frequency category*
Immune system disorders	
Hypersensitivity (including urticaria, rash, pruritus, erythema)	Common
Eye disorders	
Visual acuity reduced	Common
Retinal haemorrhage	Common
Uveitis	Common
Iridocyclitis	Common
Iritis	Common
Retinal vascular occlusion	Common
Vitreous haemorrhage	Common
Vitreous detachment	Common
Retinal tear	Common
Cataract	Common
Conjunctival haemorrhage	Common
Vitreous floaters	Common
Eye pain	Common
Intraocular pressure increase	Common
Conjunctivitis	Common
Retinal pigment epithelial tear	Common
Vision blurred	Common
Corneal abrasion	Common
Punctate keratitis	Common
Blindness	Uncommon
Endophthalmitis	Uncommon
Retinal detachment	Uncommon
Conjunctival hyperaemia	Uncommon
Lacrimation increased	Uncommon
Abnormal sensation in eye	Uncommon
Detachment of retinal pigment epithelium	Uncommon
Vitritis	Uncommon
Anterior chamber inflammation	Uncommon
Anterior chamber flare	Uncommon
Corneal oedema	Uncommon
Retinal vasculitis	Uncommon
*The frequency category for each adverse reaction is based on the most conservative incidence rate from either pooled nAMD or pooled DME Phase III studies.	

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Beovu via spontaneous case reports and literature cases. Because these reactions are reported voluntarily

from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Eye disorders
Retinal vascular occlusion, retinal vasculitis, scleritis

Description of selected adverse drug reaction

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.

Intraocular inflammation , including retinal vasculitis and/or retinal vascular occlusion

Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, has been reported with the use of Beovu (see sections 4.3 CONTRAINDICATIONS and 4.8 ADVERSE EFFECTS). A higher number of intraocular inflammation events were observed among patients with treatment-emergent antibodies. After investigation, retinal vasculitis and/or retinal vascular occlusion were found to be immune-mediated events. Intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion, may occur following the first intravitreal injection and at any time of treatment. These events were observed more frequently at the beginning of the treatment.

Intraocular inflammation incidence was approximately 4% in phase III clinical studies HAWK and HARRIER. In the phase III clinical studies KESTREL and KITE, the incidence of intraocular inflammation for brolucizumab 6 mg was approximately 3%. Based on clinical studies these events were more frequent in female patients treated with Beovu than male patients (e.g. 5.3% females vs. 3.2% males in HAWK and HARRIER) and in Japanese patients.

In patients developing these events, treatment with Beovu should be discontinued and the events should be promptly managed. Patients treated with Beovu with a medical history of intraocular inflammation and/or retinal vascular occlusion (within 12 months prior to the first brolucizumab injection) should be closely monitored, since they are at increased risk of developing retinal vasculitis and/or retinal vascular occlusion.

The interval between two Beovu doses during maintenance treatment should not be less than 8 weeks considering that a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion was reported in patients with nAMD who received Beovu every

4 week maintenance dosing in a clinical study compared to patients who received Beovu every 8 or 12 week maintenance dosing in the pivotal Phase III clinical studies.

Wet AMD

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.

DME

The pre-treatment incidence of anti-brolucizumab antibodies was 64%. After dosing with Beovu for 96 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 16 to 23% of patients.

In wet AMD and DME, among patients with treatment emergent antibodies, a higher number of intraocular inflammation events were observed. Anti-brolucizumab antibodies were not associated with an impact on clinical efficacy. Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, are immune mediated adverse events related to exposure to Beovu. This treatment emergent antibody response may develop following the first intravitreal injection (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

Wet AMD

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).

DME

In the KESTREL and KITE 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) were observed in patients treated with Beovu as early as 4 weeks after treatment initiation and up to Week 52. These reductions were maintained up to Week 100.

Clinical trials

Treatment of wet AMD

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:

- brolucizumab 3 mg administered every 12 or 8 weeks after the first 3 monthly doses;
- brolucizumab 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:

- brolucizumab 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 Table 2 and in Figure 1 below.

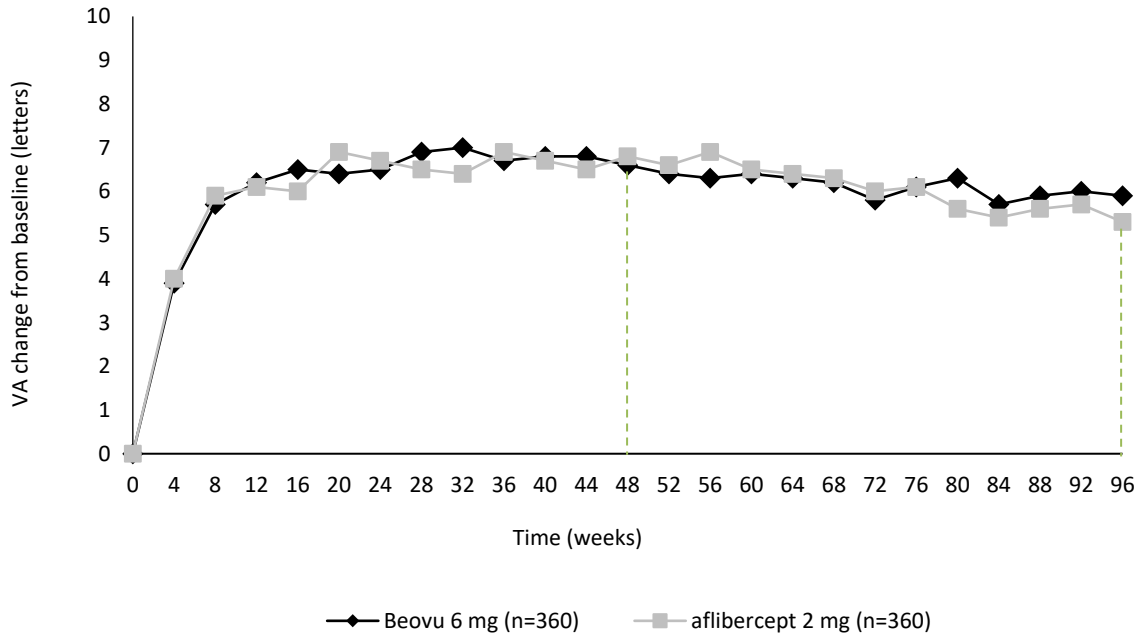
Table 2 **Visual acuity outcomes at weeks 48 and 96 in Phase III - HAWK and HARRIER studies**

		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)

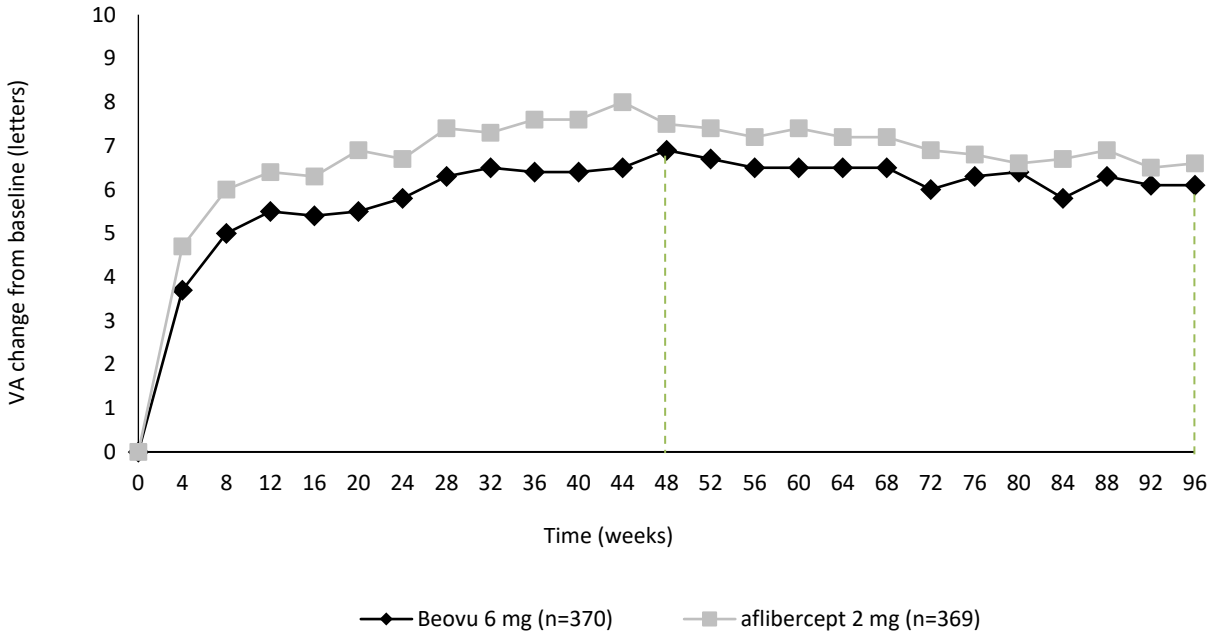
BCVA: Best Corrected Visual Acuity; missing data are imputed using last observation carried forward (LOCF) method
ETDRS: Early Treatment Diabetic Retinopathy Study[a)] P-value referring to the non-inferiority hypothesis with a non-interiority margin of 4.0 letters
[b)] Key secondary endpoint, accounting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

Treatment of DME

The safety and efficacy of Beovu were assessed in two randomised, multicentre, double-masked, active controlled, Phase III studies (KESTREL and KITE) in patients with diabetic macular oedema (DME).

A total of 926 patients were treated in these studies for 2 years (558 on brolucizumab and 368 on aflibercept 2 mg). Patient ages ranged from 23 to 87 years with a mean of 63 years.

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

- brolucizumab 6 mg administered once every 6 weeks for first 5 doses, followed by brolucizumab 6 mg every 12 or 8 weeks.
- brolucizumab 3 mg administered once every 6 weeks for first 5 doses, followed by brolucizumab 3 mg every 12 or 8 weeks.
- aflibercept 2 mg administered once every 4 weeks for first 5 doses, followed by aflibercept 2 mg every 8 weeks.

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

- brolucizumab 6 mg administered once every 6 weeks for first 5 doses, followed by brolucizumab 6 mg every 12 or 8 weeks or 16 weeks from Week 72 onwards.
- aflibercept 2 mg administered once every 4 weeks for first 5 doses, followed by aflibercept 2 mg every 8 weeks.

In both studies, after the first five doses (Weeks 0, 6, 12, 18 and 24), 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 32 and 36) and at each subsequent scheduled treatment visit. Patients who showed disease activity (e.g. decreased visual acuity, increased central subfield thickness) at any of these visits were adjusted to an every 8 weeks treatment interval. In year 2 of KITE, patients who showed no disease activity could be extended to an every 16 weeks treatment interval. The comparator aflibercept was administered every 8 weeks after the first 5 monthly doses.

Results

The primary efficacy endpoint for both studies was the change from baseline at Week 52 in Best Corrected Visual Acuity (BCVA) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score with the primary objective to demonstrate non-inferiority of Beovu versus aflibercept 2 mg. 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 results of KESTREL and KITE also demonstrated non-inferiority of Beovu versus aflibercept 2 mg for the key secondary endpoint (average change from baseline in BCVA over the period Week 40 through Week 52).

The median number of injections given over 24 months was 11 in patients treated with Beovu versus 15 in patients treated with aflibercept 2 mg.

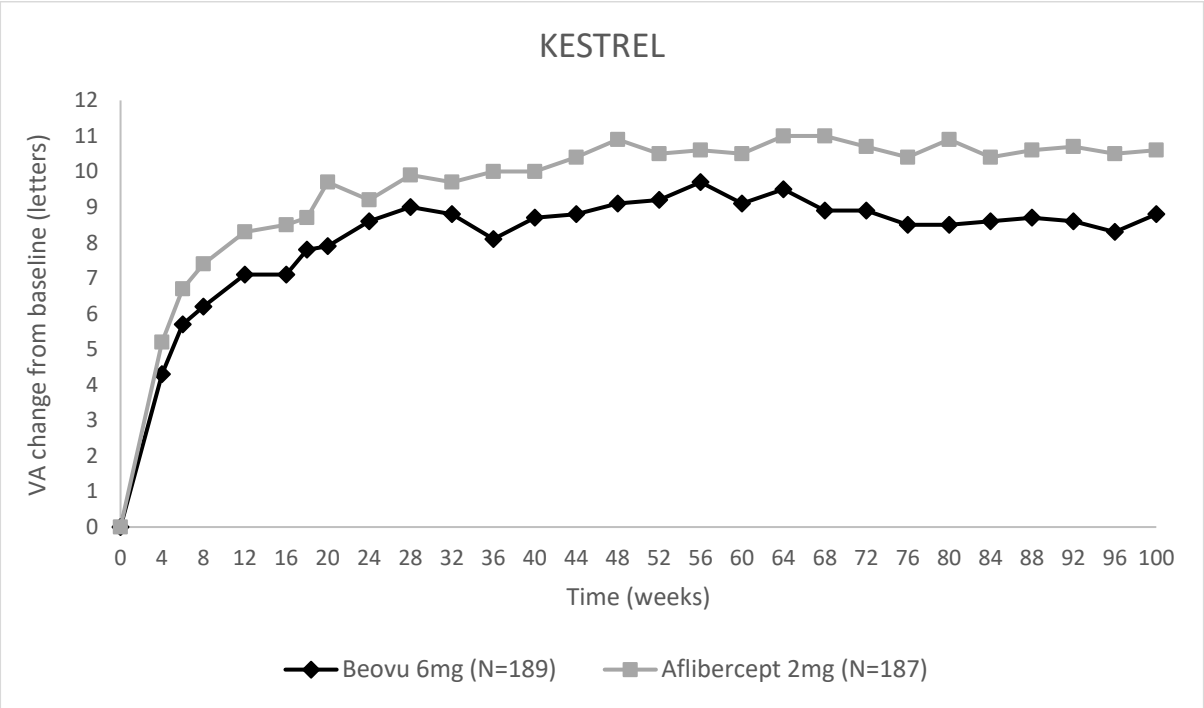
Detailed results of both studies are shown in Table 3 and Figure 2 below.

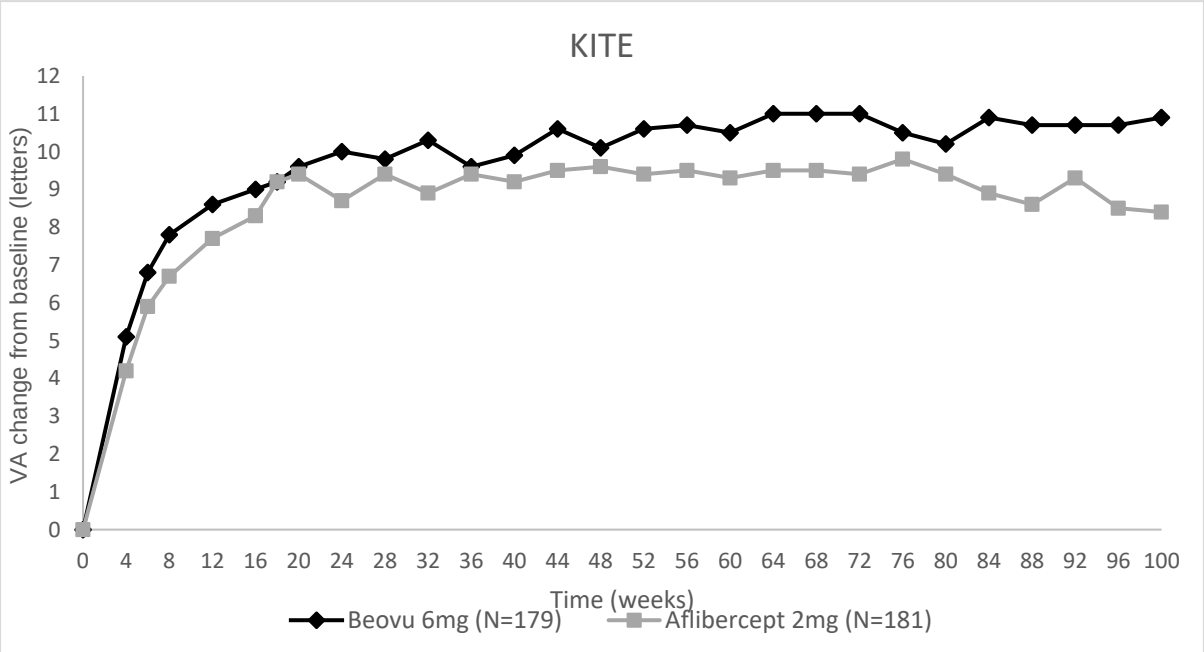
Table 3 Efficacy outcomes at Weeks 52 and 100 in Phase III - KESTREL and KITE studies

		KESTREL			KITE		
Efficacy outcome	**At Week**	**Beovu 6mg (n=189)**	**aflibercept 2 mg (n=187)**	**Difference (95% CI) Beovu – aflibercept**	**Beovu 6mg (n=179)**	**aflibercept 2 mg (n=181)**	**Difference (95% CI) Beovu – aflibercept**
Change from baseline in BCVA (measured by ETDRS letters score) – LS mean (SE)	52	9.2 (0.57)	10.5 (0.57)	-1.3 (-2.9, 0.3) P <0.001a	10.6 (0.66)	9.4 (0.66)	1.2 (-0.6, 3.1) P <0.001a
	40-52	9.0 (0.53)	10.5 (0.53)	-1.5 (-3.0, 0.0) P <0.001a	10.3 (0.62)	9.4 (0.62)	0.9 (-0.9, 2.6) P <0.001[a]
	100	8.8 (0.75)	10.6 (0.75)	-1.7 (-3.8, 0.4)	10.9 (0.85)	8.4 (0.85)	2.6 (0.2, 4.9)
Gain of at least 15 letters in BCVA from baseline or BCVA ≥84 letters (%)	52	36.0	40.1	-4.1 (-13.3, 5.9)	46.8	37.2	9.6 (-0.4, 20.2)
	100	39.2	42.2	-3.0 (-12.5, 6.3)	50.4	36.9	13.6 (3.3, 23.5)
Average change from baseline in CST (micrometers) – LS mean (SE)	40-52	-159.5 (5.88)	-158.1 (5.91)	-1.4 (-17.9, 15.0)	-187.1 (6.91)	-157.7 (6.89)	-29.4 (-48.6, -10.2) P =0.001 [b]
	88-100	-171.9 (6.18)	-168.5 (6.22)	-3.5 (-20.7, 13.8)	-196.6 (7.28)	-173.4 (7.26)	-23.2 (-43.5, -3.0)
Presence of IRF and/or SRF (%)	52	60.4	73.5	-13.2 (-23.2, -3.8)	54.5	72.9	-18.4 (-28.5, -8.3)
	100	41.8	54.2	-12.4 (-22.8, -2.1)	40.7	56.9	-16.2 (-26.4, -5.9)

BCVA: Best Corrected Visual Acuity; BCVA assessments after start of alternative DME treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment
CST: Central subfield thickness
IRF: Intraretinal fluid; SRF: Subretinal fluid
CST and fluid status assessments after start of alternative DME treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment
[a] P-value referring to the non-inferiority hypothesis with a non-inferiority margin of 4 letters
[b] P-value referring to the superiority testing at one-sided type I error of 0.025

Figure 2 **Mean change in visual acuity from baseline to Week 100 in KESTREL and KITE studies**





These visual acuity gains were achieved with 55% and 50% of patients treated with Beovu on a 12-weekly dosing interval at Week 52, and 44% and 37% of patients treated with Beovu on a 12-weekly or 12-weekly/16-weekly dosing interval at Week 100 in KESTREL and KITE, respectively. Among patients identified as eligible for the 12-weekly dosing during the first 12-week interval, approximately 70% remained on at least the 12-weekly dosing interval at Week 100 in both studies. In KITE, 25% of patients were treated with Beovu on a 16-weekly dosing interval at Week 100.

Treatment effects in evaluable subgroups (i.e. age, gender, baseline HbA1c, baseline visual acuity, baseline central subfield thickness, DME lesion type, duration of DME since diagnosis, retinal fluid status) in each study were generally consistent with the results in the overall population.

In KESTREL and KITE, disease activity (DA) was assessed throughout the studies by changes in visual acuity and/or anatomical parameters, including CST and/or presence of IRF/SRF. At the first assessment at Week 32, disease activity was observed in 20.1% and 24.2% of patients treated with Beovu (5 injections received) and 27.8% and 39.8% of patients treated with aflibercept 2 mg (6 injections received) in KESTREL and KITE, respectively.

In both studies, Beovu demonstrated a significant reduction from baseline in CST starting at Week 4 and continuing up to Week 52. In KITE, the average reduction from baseline over the period Week 40 to Week 52 with Beovu was statistically superior to that observed with aflibercept 2 mg. From Week 40 to Week 52 in both studies, the proportion of patients with IRF/SRF was lower in patients treated with Beovu (range 54% to 65%) compared to patients treated with aflibercept 2 mg (range 71% to 80%). The reduction in CST from baseline was maintained up to Week 100. At Week 100, the proportion of patients with IRF/SRF was lower in patients treated with Beovu (42% KESTREL and 41% KITE) compared to patients treated with aflibercept 2 mg (54% KESTREL and 57% KITE).

In both studies, Beovu demonstrated 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 Best Corrected Visual Acuity (BCVA).

No differences were found between Beovu and aflibercept 2 mg in changes from baseline to Week 52 and to Week 100 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).

Diabetic retinopathy severity score (DRSS) was assessed in the KESTREL and KITE studies. At baseline, 98.1% of patients in both KESTREL and KITE had gradable DRSS scores. Based on the pooled analysis, 28.9% of patients treated with Beovu experienced a ≥2 step improvement from baseline to Week 52 in the DRSS score compared to 24.9% of patients treated with aflibercept 2 mg. The estimated difference between Beovu and aflibercept 2 mg was 4.0% (95% CI: [-0.6, 8.6]). At Week 100, the proportion of patients with a ≥2 step improvement from baseline to Week 100 in the DRSS score was 32.8% with Beovu and 29.3% with aflibercept 2mg in KESTREL and 35.8% with Beovu and 31.1% with aflibercept 2mg in KITE.

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 4.3 $\pm$ 1.9 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. In the KESTREL and KITE clinical studies, approximately 45% (164/368) of patients randomised to treatment with Beovu were ≥ 65 years of age and approximately 10% (37/368) 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 humanised 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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® = Registered trademark

9 DATE OF FIRST APPROVAL

16 January 2020

10 DATE OF REVISION

19 June 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Adverse drug reactions from spontaneous reports and literature cases (frequency not known)- Eye disorders- Addition of scleritis

Internal document code: beo190624i based on CDSv1.10 dated 15 Feb 2024