Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

PAGENAX 120 MG/ML solution for injection

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

2. Qualitative and quantitative composition

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

One mL solution for injection contains 120 mg of brolucizumab.

Vial
Each vial contains 27.6 mg of 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.

Pre-filled syringe

Each pre-filled syringe contains 19.8 mg of 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**.**

Excipients with Known Effects

5.8% sucrose

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

Beovu®/™ is supplied in a single-use vial or in a single-use pre-filled syringe.

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

Pre-filled syringe
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 edema (DME).

4.2 Posology and method of administration

Single-use vial or single-use pre-filled syringe for intravitreal use only. Each vial or pre-filled syringe should only be used for the treatment of a single eye.
Beovu must be administered by a qualified physician.

Posology

General target population

Wet AMD

Treatment initiation – loading

The recommended dose for Beovu is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first three doses. Alternatively, Beovu may be administered every 6 weeks for the first two doses, and a third dose may be administered 6 weeks later based on an assessment of disease activity.

Maintenance treatment

After the last loading dose, Beovu is administered every 12 weeks (3 months). The physician may then individualize treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. The treatment interval could be as frequent as every 8 weeks (2 months). If patients are being treated according to a treat-and-extend regimen and there are no signs of disease activity, the treatment intervals could be extended stepwise until signs of disease activity recur. The treatment interval should be extended or shortened by no more than 4 weeks at a time. However, the interval between two doses should not be less than every 8 weeks (2 months) (see sections 4.4 and 5.1).

Diabetic Macular Edema (DME)

The recommended dose for Beovu is 6 mg (0.05 mL) administered by intravitreal injection every 6 weeks for the first five doses. Thereafter, Beovu is administered every 12 or 16 weeks (3 or 4 months). Treatment intervals should be determined by the physician and should be based on disease activity as assessed by visual acuity and/or anatomic

parameters. In patients with disease activity, treatment every 8 weeks (2 months) could be considered (see section 5.1) .

Special populations

Renal impairment
No dosage adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment
Brolucizumab has not been studied in patients with hepatic impairment. No dosage adjustment is required in patients with hepatic impairment (see section 5.2).

Pediatric patients (below 18 years)
The safety and efficacy of Beovu in pediatric patients have not been established.

Geriatric patients (65 years or above)
No dosage regimen adjustment is required in patients 65 years or above.

As with all medicinal products for intravitreal use, Beovu should be inspected visually prior to administration (see section 6.6).

The injection procedure must be carried out under aseptic conditions, which include 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. Patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see section 4.3). Adequate anesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

For information on preparation of Beovu, see Instructions for use, see section 6.6.

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.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

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.
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).

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

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 of 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).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with active or suspected ocular or periocular infections.

Patients with active intraocular inflammation.

4.4 Special warnings and precautions for use

Endophthalmitis, retinal detachment, retinal vasculitis and/or retinal vascular occlusion

Intravitreal injections, including those with Beovu, have been associated with endophthalmitis, and retinal detachment. Proper aseptic injection techniques must always be used when administering Beovu.

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, 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 (see sections 4.3 Contraindications and 4.8 Adverse drug reactions).

Patients should be instructed to report any symptoms suggestive of the above mentioned events without delay.

In a Phase IIIa clinical study (MERLIN), patients with nAMD who received Beovu every 4 week 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). The interval between two Beovu doses during maintenance treatment should not be less than 8 weeks (see section 4.2 posology and administration).

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 drug reactions). 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.

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). 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).

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed

4.6 Pregnancy and Lactation

Pregnancy

Risk summary

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.

A study in pregnant cynomolgus monkeys did not indicate any harmful effects with respect to pre- or postnatal development at approximately 6-times the human exposure based on serum Cmax (see Animal data). However, based on the anti-VEGF mechanism of action, brolucizumab must be regarded as potentially teratogenic and embryo/fetotoxic.

Therefore, Beovu should not be used during pregnancy unless the expected benefits outweigh the potential risks to the fetus.

Animal data
In an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys, brolucizumab was administered to all animals by intravitreal (IVT) injection to one eye at doses of 3 or 6 mg once every 4 weeks until delivery. One additional injection was administered to a subset of animals 28 days post-partum and these animals had blood and milk collected for toxicokinetic evaluations. There was no impact of IVT administration of brolucizumab on embryo-fetal 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 Cmax) at the proposed clinical dose of 6 mg . 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 to female reproduction and to embryo-fetal development.

Lactation
It is unknown if brolucizumab is transferred into human milk after administration of Beovu. There are no data on the effects of Beovu on the breastfed child 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 breastfed child, breastfeeding is not recommended

during treatment and 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 brolucizumab therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Females of reproductive potential

Females of reproductive 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, and should therefore be advised not to drive or use machinery until visual function has recovered sufficiently.

4.8 Undesirable effects

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.

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

Less common serious adverse drug reactions reported in <1% of the patients treated with Beovu 6 mg were endophthalmitis, 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 summary of adverse drug reactions from clinical trials

Adverse drug reactions from the HAWK and HARRIER clinical trials (Table 7-1) 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 drug 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).

Table **Error! No text of specified style in document.**-1

Percentage of patients with adverse drug reactions in HAWK and HARRIER 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	2.7	1.1	Common

Adverse drug reactions	Beovu (N=730)	Aflibercept (N=729)	Frequency category
tear			
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
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

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 categorized 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.

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Eye disorders
Retinal vascular occlusion, retinal vasculitis

Description of selected adverse drug reactions

Intraocular inflammation

Based on clinical studies, intraocular inflammation related adverse events, including retinal vasculitis and retinal vascular occlusion, were reported more frequently in female patients treated with Beovu than male patients (e.g., 5.3% females vs. 3.2% males in HAWK and HARRIER).

The results of a retrospective real world evidence analysis in nAMD patients who were evaluated for up to 6 months after initiating treatment with Beovu suggest that patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with Beovu were more likely to present with similar events after Beovu injection, as compared to nAMD patients with no history of these events.

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.

Pre-treatment antibodies have been detected in drug-naïve subjects for a variety of biotechnology-derived therapeutic proteins including single-chain antibodies.

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 to 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, anti-brolucizumab antibodies were not associated with an impact on clinical efficacy. Among patients with treatment-emergent antibodies, a higher number of intraocular inflammation events were observed. 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 4.4 Warnings and precautions).

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Antineovascularization agents.

ATC code: S01LA06

Mechanism of action (MOA)

Brolucizumab is a humanised monoclonal single chain Fv (scFv) antibody fragment with a molecular
weight of ~26 kDa.

Increased levels of signaling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathologic ocular angiogenesis and retinal edema. Brolucizumab binds with high affinity to VEGF-A isoforms (e.g., VEGF110, VEGF121, and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF A binding, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathologic neovascularization and decreasing vascular permeability.

Pharmacodynamics (PD) effects

Wet AMD

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 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 (see section Clinical studies).

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.

Treatment of wet AMD

Clinical efficacy and safety

The safety and efficacy of Beovu were assessed in two randomized, multi-center, 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 randomized in a 1:1:1 ratio to the following dosing regimens:

- brolucizumab 3 mg administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses,
- brolucizumab 6 mg administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses,
- aflibercept 2 mg administered every 8 weeks (q8w) after the first 3 monthly doses.

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

- brolucizumab 6 mg administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses,
- aflibercept 2 mg administered every 8 weeks (q8w) after the first 3 monthly doses.

In both studies, after the first three monthly doses (Week 0, 4 and 8), brolucizumab patients were treated q12w, with the option of adjusting

to q8w dosing interval based on disease activity. Disease activity was assessed by a physician during the first q12 week interval (at Week 16 and 20) and at each subsequent scheduled q12w treatment visit. Patients who showed disease activity (e.g., decreased visual acuity, increased central subfield thickness (CST), and/or presence of retinal fluids (IRF/SRF, sub-RPE)) at any of these visits were adjusted to a q8w treatment interval.

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 to demonstrate non-inferiority of Beovu vs. aflibercept. In both studies, Beovu (administered in a q12w/q8w regimen) demonstrated non-inferior efficacy to aflibercept 2 mg (administered q8w). The visual acuity gains observed in the first year were maintained in the second year.
Detailed results of both studies are shown in Table 12-1 and Figure 12-1 below

*Table **Error! No text of specified style in document.**-2 Visual acuity outcomes at Week 48 and 96 in Phase III - HAWK and HARRIER studies*

		HAWK			**HARRIER**		
Efficacy outcome	**At week**	**Beovu (n=360)**	**Aflibercept 2 mg (n=360)**	**Difference (95% CI) brolucizumab – aflibercept**	**Beovu (n=370)**	**Aflibercept 2 mg (n=369)**	**Difference (95% CI) brolucizumab – aflibercept**
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)

		HAWK			HARRIER		
Efficacy outcome	**At week**	**Beovu (n=360)**	**Aflibercept 2 mg (n=360)**	**Difference (95% CI) brolucizumab – aflibercept**	**Beovu (n=370)**	**Aflibercept 2 mg (n=369)**	**Difference (95% CI) brolucizumab – aflibercept**
% 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

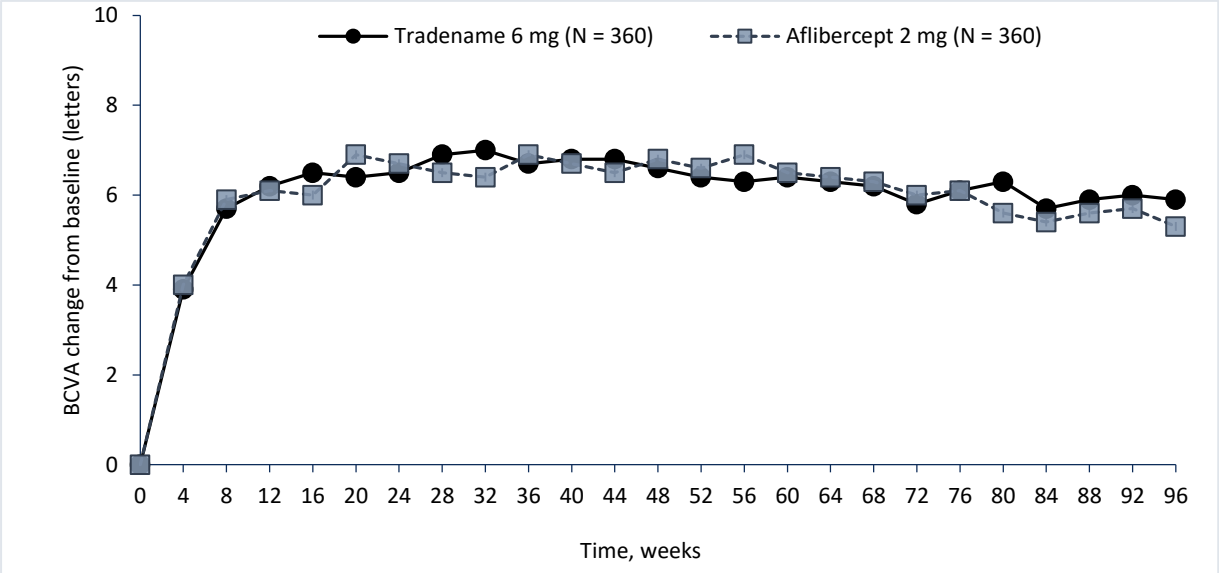
ETDRS: Early Treatment Diabetic Retinopathy Study

[a] P-value referring to the non-inferiority hypothesis with a non-interiority margin of 4.0 letters

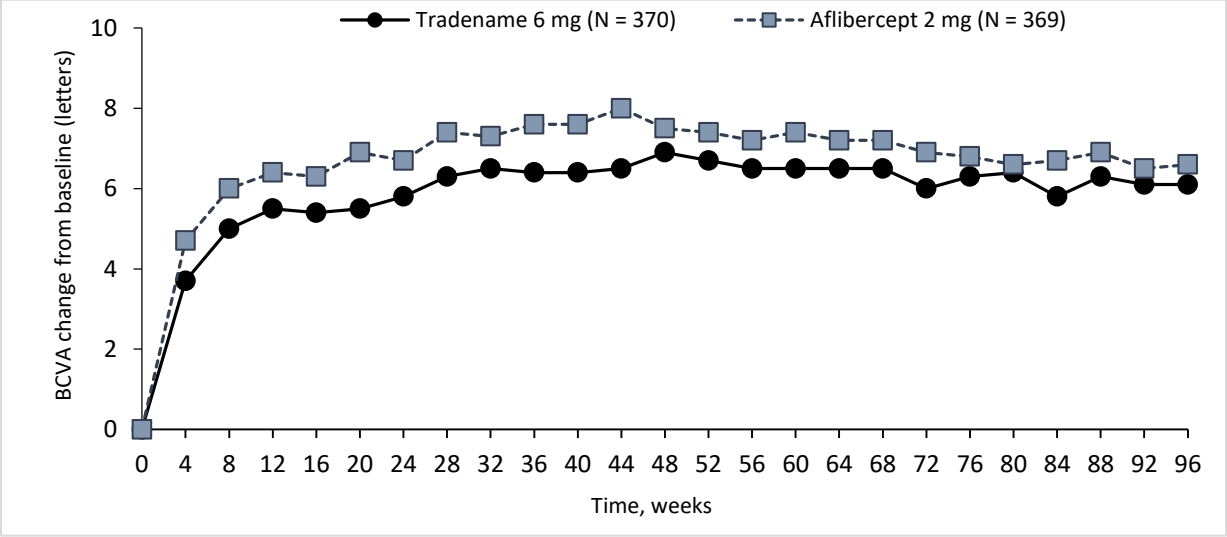
[b] Key secondary endpoint, accounting for differences in timing of Beovu and aflibercept treatments

*Figure **Error! No text of specified style in document.**-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% patients treated with Beovu on q12w 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 q12w interval during the first 12 week interval, 85% and 82% remained on the q12w dosing interval up to Week 48. Of patients on the q12w interval at Week 48, 82% and 75% remained on the 12 week dosing interval through Week 96.

Table **Error! No text of specified style in document.**-3 Disease Activity Evaluation in HAWK and HARRIER studies up to Week 96

		HAWK			**HARRIER**		
Efficacy outcome (pre-specified secondary endpoints)	**At Week**	**Beovu (N=360)**	**Aflibercept 2mg (N=360)**	**Difference (95% CI) brolucizumab – aflibercept**	**Beovu (N=370)**	**Aflibercept 2mg (N=369)**	**Difference (95% CI) brolucizumab – aflibercept**
% of patients with disease activity [c]	16[d]	24.0	34.5	-10.5 (-17.1, -3.5) P=0.0013[a]	22.7	32.2	-9.5 (-15.8, -3.1) P=0.0021[a]
Mean change in CST from baseline (µm)	16[d]	-161.4 (SE=6.2)	-133.6 (SE=6.2)	-27.8 (-45.1, -10.5) P=0.0008 [a]	-174.4 (SE=6.7)	-134.2 (SE=6.7)	-40.2 (-58.9, -21.6) P<0.0001 [a]
	48	-172.8 (SE=6.7)	-143.7 (SE=6.7)	-29.0 (-47.6, -10.4) P=0.0012[a]	-193.8 (SE=6.8)	-143.9 (SE=6.8)	-49.9 (-68.9, -30.9) P<0.0001[a]
	96	-174.8 (SE=7.3)	-148.7 (SE=7.3)	-26.0 (-46.2, -5.9) P=0.0115[b]	-197.7 (SE=7.0)	-155.1 (SE=7.0)	-42.6 (-62.0, -23.3) P<0.0001 [b]
% of patients with IRF and/or SRF fluid	16 [d]	33.9	52.2	-18.2 (-25.3, -10.9) P<0.0001 [a]	29.4	45.1	-15.7 (-22.9, -9.0) P<0.0001[a]
	48	31.2	44.6	-13.5 (-20.7, -6.1) P=0.0001 [a]	25.8	43.9	-18.1 (-24.9, -11.8) P<0.0001[a]

		HAWK			HARRIER		
Efficacy outcome (pre-specified secondary endpoints)	**At Week**	**Beovu (N=360)**	**Aflibercept 2mg (N=360)**	**Difference (95% CI) brolucizumab – aflibercept**	**Beovu (N=370)**	**Aflibercept 2mg (N=369)**	**Difference (95% CI) brolucizumab – aflibercept**
	96	24.0	36.9	-12.9 (-19.7, -6.6) P=0.0002[b)]	24.4	38.5	-14.1 (-21.3, -7.2) P<0.0001[b)]
% of patients with sub-RPE fluid	16[d)]	18.7	27.3	-8.6 (−14.4, −2.9) P=0.0030[b)]	16.0	23.8	-7.8 (−13.0, −2.7) P=0.0041[b)]
	48	13.5	21.6	-8.1 (−13.6, −2.7) P=0.0035[b)]	12.9	22.0	-9.1 (−13.8, −3.9) P=0.0007[b)]
	96	10.9	14.7	-3.8 (-8.5, 0.8) P=0.1213[b)]	16.5	22.4	-5.9 (-11.5, -0.3) P=0.0371[b)]

CST: Central subfield thickness; IRF/SRF: Intraretinal/subretinal fluid; RPE: Retinal pigment epithelium;

[a)] Secondary endpoint in HARRIER, confirmatory analysis in HAWK; 1-sided p-values for superiority of brolucizumab

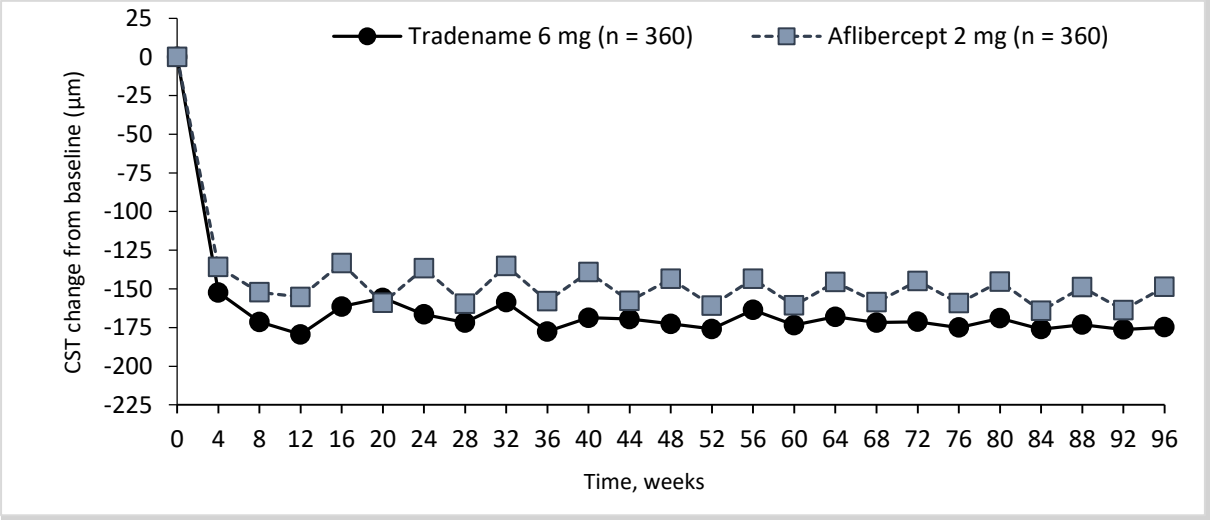
[b)] Secondary endpoints in HAWK and HARRIER; 2-sided p-values

[c)] Disease activity assessments were based on the physician's judgment supported by protocol guidance at Week 16: Decrease in BCVA of ≥ 5 letters compared with baseline, decrease in BCVA of ≥ 3 letters and CST increase ≥75 µm compared with Week 12, decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 12 or new or worse intraretinal cysts (IRC)/intraretinal fluid (IRF) compared with Week 12

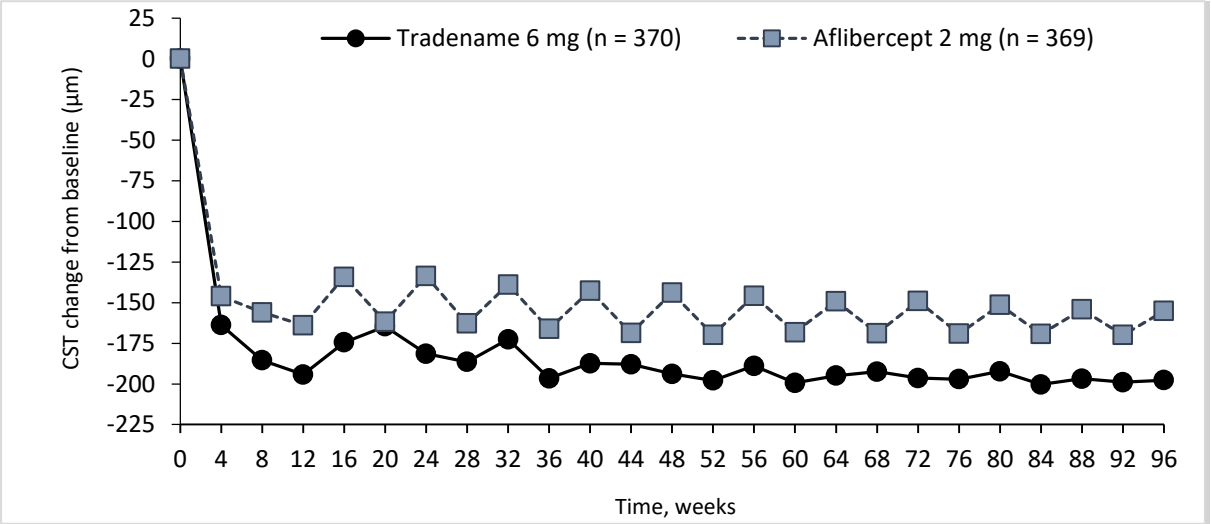
[d)] Up to Week 16, treatment exposure was identical, allowing a matched comparison of Beovu and aflibercept

Figure 12-2 Central subfield thickness change from baseline to Week 96 in HAWK and HARRIER studies

HAWK



HARRIER



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 Best Corrected Visual Acuity (BCVA). Patient reported outcomes 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, color vision, and peripheral

vision).
In silico study
The results of the Beovu arms of the HAWK and HARRIER studies, where Beovu was administered every 4 weeks (monthly) for the first 3 doses followed by dosing every 12 or 8 weeks (q12w/q8w), were replicated in a population PK/PD model simulation study where Beovu was administered every 6 weeks (q6w) for the first 2 doses followed by dosing every 12 or 8 weeks (q12w/q8w).
TALON study
A treat and extend dosing regimen for the maintenance phase was examined in the TALON study, which was a 64-week two-arm, randomized, double-masked, multi-center, phase IIIb study assessing the efficacy and safety of Beovu compared to aflibercept 2 mg in patients with nAMD.
737 patients were randomized in a 1:1 ratio to one of the two treatment arms, either brolucizumab 6 mg or aflibercept 2 mg. Patients in both treatment arms were dosed once every 4 weeks (q4w) for the first 3 injections and then one injection after 8 weeks. Thereafter, treatment intervals were either every 8 weeks, every 12 weeks, or every 16 weeks up to Week 60 or 62.
The study had two primary objectives and related endpoints: 1) to demonstrate that Beovu is superior to aflibercept 2 mg with respect to the duration of treatment intervals at Week 32, as assessed by the distribution of the last interval with no disease activity up to Week 32. 2) to demonstrate that Beovu is non-inferior to aflibercept 2 mg with respect to the average change in BCVA from baseline at Weeks 28 and 32, as assessed by the average change in BCVA from baseline at Weeks 28 and 32.
The study met its co-primary efficacy endpoints. 1) Beovu demonstrated superiority to aflibercept 2 mg at Week 32 for the distribution of the last interval with no disease activity. The last intervals with a duration of 12-weeks, 8-weeks, 4-weeks were 38.5%, 35.8%, and 25.7% for Beovu vs. 19.8%, 39.9%, and 40.2% for aflibercept 2 mg, respectively (p-value <0.0001). 2) Beovu demonstrated non-inferiority to aflibercept 2 mg for the average change in BCVA from baseline at Weeks 28 and 32 (+5.2 ETDRS letters vs +5.1 ETDRS letters for Beovu and aflibercept 2 mg, respectively; LS mean difference 0.1, 95% CI: [-1.3, 1.5], p-value < 0.0001).
At Week 64 the distribution of the last treatment interval with no disease activity with a duration of 16-weeks, 12-weeks, 8-weeks, 4-weeks was 28.4%, 22.4%, 26.0%, 23.2% for Beovu vs. 12.2%, 23.9%, 22.0%, 41.8% for aflibercept, respectively. The average change in BCVA from baseline at Week 64 were +4.7 ETDRS letters vs. +4.9 ETDRS letters for Beovu and aflibercept 2mg, respectively; LS mean difference –0.2, 95% CI: [-1.9, 1.5].
Patients who needed more frequent treatment interval than 8 weeks were discontinued from the study treatment (see section 6

Warnings and precautions) and were treated with standard of care. These patients were categorized in the 4-week group for the purpose of treatment distribution assignment.
At Weeks 28 and 32, the average change in CST was greater with Beovu vs. aflibercept (LS mean difference -26.9 µm, 95% CI: [-46.3, -7.5]). At Week 32, the percentage of patients with IRF and/or SRF fluid and sub-RPE fluid was less with brolucizumab vs. aflibercept (50.3% vs. 56.9% and 54.2% vs. 65.8%). These results were consistent at week 64 (CST -15.4µm, 95% CI: [-37.6 6.7]; IRF and/or SRF 26.6% vs. 34.4%; Sub-RPE12.5% vs. 17.8%).

Treatment of DME

The safety and efficacy of Beovu were assessed in two randomized, multi-center, double-masked, active controlled, Phase III studies (KESTREL and KITE) in patients with diabetic macular edema (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 randomized in a 1:1:1 ratio to the following dosing regimens:

- brolucizumab 6 mg administered once every 6 weeks (q6w) for first 5 doses, followed by brolucizumab 6 mg every 12 or 8 weeks (q12w/q8w).
- brolucizumab 3 mg administered once every 6 weeks (q6w) for first 5 doses, followed by brolucizumab 3 mg every 12 or 8 weeks (q12w/q8w).
- aflibercept 2 mg administered once every 4 weeks (q4w) for first 5 doses, followed by aflibercept 2 mg every 8 weeks (q8w).

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

- brolucizumab 6 mg administered once every 6 weeks (q6w) for first 5 doses, followed by brolucizumab 6 mg every 12 or 8 weeks (q12w/q8w) or 16 weeks from Week 72 onwards (q16w).
- aflibercept 2 mg administered once every 4 weeks (q4w) for first 5 doses, followed by aflibercept 2 mg every 8 weeks (q8w).

In both studies, after the first five doses (Weeks 0, 6, 12, 18 and 24), brolucizumab patients were treated q12w, with the option of adjusting to a q8w dosing interval based on disease activity. Disease activity was assessed by a physician during the first q12 week interval (at Weeks 32 and 36) and at each subsequent scheduled q12w treatment visit. Patients who showed disease activity (e.g., decreased visual acuity, increased central subfield thickness) at any of these visits were adjusted to a q8w treatment interval. In year 2 of KITE, patients who showed no disease activity could be extended to a q16w 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 a q12w/q8w regimen) demonstrated non-inferior efficacy to aflibercept 2 mg (administered q8w).

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 12-3 and Figure 12-3 below.

Table 12-3 Efficacy outcomes at Weeks 52 and 100 in Phase III - KESTREL and KITE studies

		KESTREL			KITE		
Efficacy outcome	**At week**	**Beovu (n=189)**	**aflibercept 2 mg (n=187)**	**Difference (95% CI) Beovu – aflibercept**	**Beovu (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 <0.001[a]	10.6 (0.66)	9.4 (0.66)	1.2 (-0.6, 3.1) P <0.001[a]
	40-52	9.0 (0.53)	10.5 (0.53)	-1.5 (-3.0, 0.0) P <0.001[a]	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

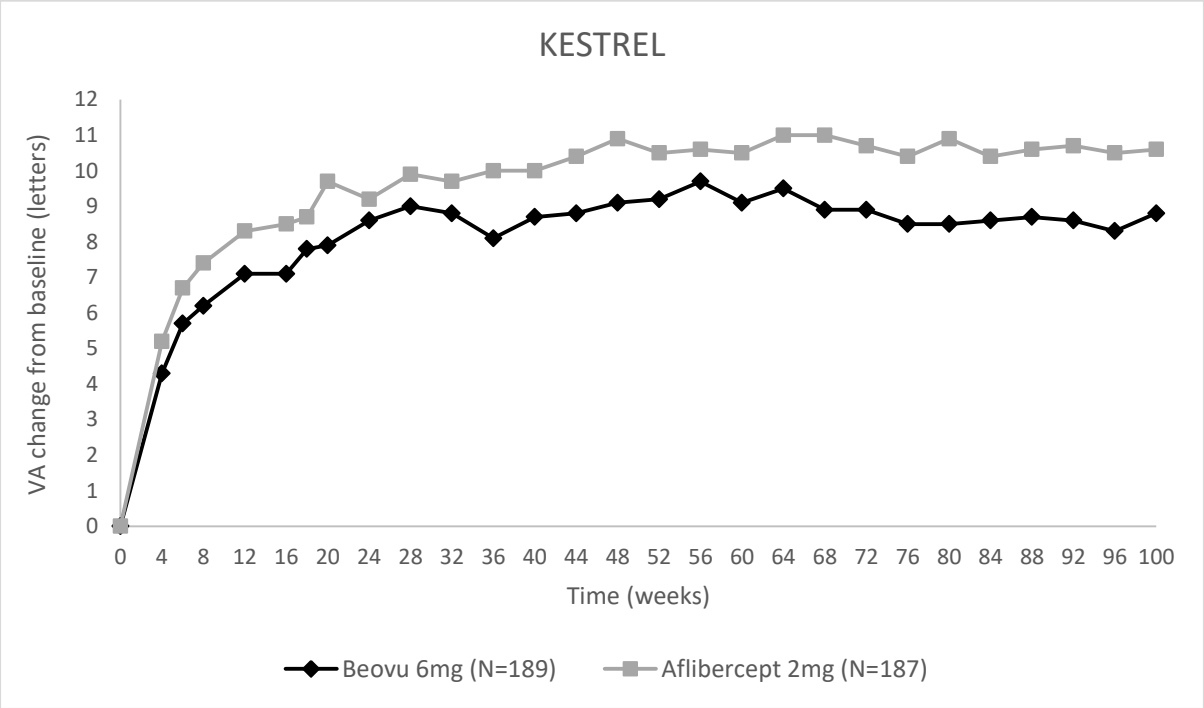
CST: Central subfield thickness

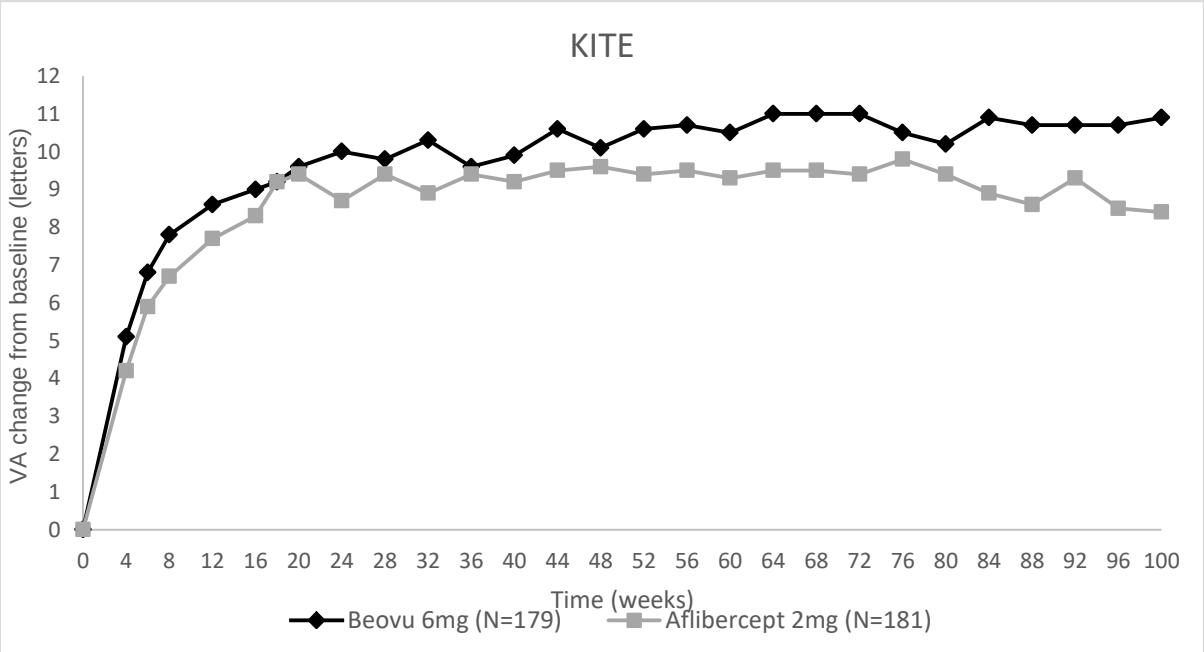
IRF: Intraretinal fluid; SRF: Subretinal fluid

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 12-3 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 q12w dosing interval at Week 52, and 44% and 37% of patients treated with Beovu on a q12w or q12w/q16w dosing interval at Week 100 in KESTREL and KITE, respectively. Among patients identified as eligible for q12w dosing during the first 12-week interval, approximately 70% remained on at least the q12w dosing interval at Week 100 in both studies. In KITE, 25% of patients were treated with Beovu on a q16w 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 KESTREL and KITE 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). Taken together, the results from both studies confirm that Beovu 6 mg and aflibercept 2 mg provide similar improvements in the VFQ-25 scores over two years of treatment.

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]) [18]. 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 2 mg in KESTREL and 35.8% with Beovu and 31.1% with aflibercept 2 mg in KITE.

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 Cmax of free brolucizumab in the plasma was 49.0 ng/mL (range: 8.97 to 548 ng/mL) and was attained in 1 day.

Metabolism/Elimination

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 ± 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

Geriatric patients (65 years or above)

In the HAWK and HARRIER clinical studies, approximately 90% (978/1,088) of patients randomized 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 randomized 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 to 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 to 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

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

Carcinogenicity and mutagenicity
No studies have been conducted on the carcinogenic or mutagenic potential of Beovu.

Repeat dose toxicity

Non-clinical data reveal no special hazard for humans based on 3- and 6-month repeated dose toxicity studies. Intravitreal injections of brolucizumab to cynomolgus monkeys at doses up to 6 mg per eye every 4 weeks for 26 weeks resulted in no ocular or systemic effects and were well-tolerated.

Evaluations included daily observations for morbidity and mortality, clinical observations (including abnormal respiration and behavior), body weight determinations, biomicroscopic and indirect ophthalmoscopic examinations, intraocular pressure measurements, electroretinograms, clinical pathology, toxicokinetic and anti-drug antibody analysis of the serum and vitreous, and macroscopic and microscopic examinations.

The ocular and systemic no observed adverse effect level (NOAEL) with brolucizumab 6 mg per eye every 4 weeks provides a 2-fold margin of ocular safety (based on comparative ocular volume) for the recommended human dose.

6. Pharmaceutical Particulars

6.1 List of Excipients

10 mM sodium citrate, 5.8% sucrose, 0.02% polysorbate 80 and water for injection and has a pH of approximately 7.2.

6.2 Incompatibilities

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

6.3 Shelf-Life

Pre-filled syringe: 18 months
Vial: 2 years

6.4 Special Precautions for storage

Vial

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
Prior to use, the unopened vial may be kept at room temperature (25°C) for up to 24 hours.
Do not freeze.
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.
Information might differ in some countries.

Pre-filled syringe

Store in a refrigerator 2°C to 8°C (36°F to 46°F).
Prior to use, the unopened blister may be kept at room temperature (25°C) for up to 24 hours.
Do not freeze.
Keep the pre-filled syringe in its sealed blister and in the 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.
Information might differ in some countries.

6.5 Nature and Content of container

Pre-filled syringe

0.165 ml sterile solution in a pre-filled syringe (type I glass) with a bromobutyl rubber plunger stopper and a syringe cap consisting of a white, tamper-evident rigid seal with a grey bromobutyl rubber tip cap including a Luer lock adapter. The pre-filled syringe has a plunger rod and a purple finger grip, and is packed in a sealed blister.

Pack size of 1 pre-filled syringe.

Vial

0.230 ml sterile solution in a 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).

6.6 Special precautions for disposal and other handling

Instructions for use of the Beovu vial kit

Storage and inspection

Store Beovu in the refrigerator (2°C to 8°C/36°F to 46°F); do not freeze. Keep the vial in the outer carton to protect from light.

Prior to use, the unopened vial of Beovu may be kept at room temperature (below 25°C/77°F) for up to 24 hours. After opening the vial, proceed under aseptic conditions.

Beovu is a clear to slightly opalescent and colorless to slightly brownish-yellow solution.

The solution should be inspected visually upon removal from the refrigerator and prior to administration. If particulates or cloudiness are visible, the vial must not be used and appropriate replacement procedures followed.

The contents of the vial and filter needle are sterile and for single use only. Do not use if the packaging, vial and/or filter needle are damaged or expired.

How to prepare and administer Beovu

The intravitreal injection procedure must 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) and the availability of sterile paracentesis equipment (if required). Adequate anesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

For preparation and intravitreal injection, the following single use medical devices are needed:

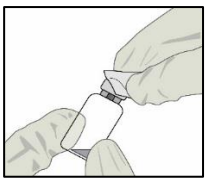
- A 30G x ½" injection needle, sterile.
- A 1 mL syringe with a 0.05 mL dose mark, sterile
- The 5 µm blunt filter needle (18G x 1½", 1.2 mm x 40 mm), sterile

The injection needle and the syringe are not included in the Beovu vial kit.

Note: The dose must be set to 0.05 mL.

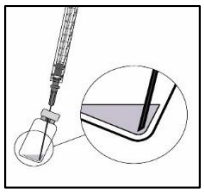
Ensure that the injection is given immediately after preparation of the dose (Step 8).

Injection procedure

1  Remove the vial cap and clean the vial septum (e.g., with 70% alcohol swab).

2 Assemble the **filter needle** onto a **1 mL syringe** using aseptic technique.

3 Push **the filter needle** into the center of the vial septum until the needle touches the bottom of the vial.

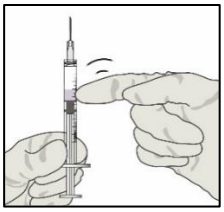
4  To withdraw the liquid, hold the vial **slightly inclined and slowly withdraw** all the liquid from the vial and filter needle.

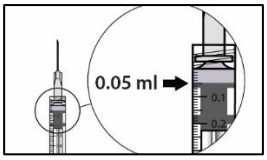
Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

5 Disconnect the filter needle from the syringe in an aseptic manner and dispose of it.

The filter needle is not to be used for intravitreal injection.

6 Aseptically and **firmly assemble a 30G x ½" injection needle** onto the syringe.

7  To check for air bubbles, hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

8 

Carefully expel the air from the syringe and adjust the dose to the 0.05 mL mark. The syringe is ready for the injection.

9 Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. **Confirm delivery of the full dose** by checking that the rubber stopper has reached the end of the syringe barrel.

Note: Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

7. Marketing Authorization Holder

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland.

8. Marketing Authorization Number

CTD10072

9. Date of first authorization/renewal of the authorization

12/09/2023

10. Date of revision of the text

11/5/2025