SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Brolucizumab 120mg/ml solution for injection
Pagenax

2. Qualitative and quantitative composition

One ml solution for injection contains 120mg of brolucizumab*.
* Brolucizumab is a humanised monoclonal single-chain Fv (scFv) antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology.
Pagenax 120mg/ml solution for injection in pre-filled syringe
Each pre-filled syringe contains 19.8mg brolucizumab in 0.165 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml solution containing 6mg of brolucizumab.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection (injection).
Clear to slightly opalescent, colourless to slightly brownish-yellow aqueous solution.

4. Clinical particulars

4.1 Therapeutic indications

Pagenax is indicated in adults for the treatment of
• neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
• visual impairment due to diabetic macular oedema (DME) (see section 5.1).

4.2 Posology and method of administration

Pagenax must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Posology
Wet AMD
The recommended dose is 6mg brolucizumab (0.05 ml solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered (see sections 4.4 and 5.1).
If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Pagenax should be discontinued.
DME
The recommended dose is 6mg 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.

If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Pagenax should be discontinued.

Special populations

Elderly

No dosage adjustment is required in patients aged 65 years or above (see section 5.2).

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).

Paediatric population

The safety and efficacy of brolucizumab in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

Pagenax is for intravitreal use only.

The solution for injection should be inspected visually prior to administration (see section 6.6).

The intravitreal 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). 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.

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. 6mg brolucizumab).

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Endophthalmitis, intraocular inflammation, traumatic cataract, retinal detachment, retinal tear, retinal vasculitis, and/or retinal vascular occlusion

Intravitreal injections, including those with Pagenax, have been associated with endophthalmitis, intraocular inflammation, traumatic cataract, retinal detachment and retinal tear (see section 4.8). Proper aseptic injection techniques must always be used when administering Pagenax.

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

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 Pagenax (see sections 4.3 and 4.8). 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.

Based on clinical studies these events were more frequent in female patients treated with Pagenax 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 Pagenax should be discontinued and the events should be promptly managed. Patients treated with Pagenax 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 Pagenax 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 Pagenax every 4 week maintenance dosing in a clinical study compared to patients who received Pagenax every 8 or 12 week maintenance dosing in the pivotal Phase III clinical studies.

Intraocular pressure increases

Transient increases in intraocular pressure have been seen within 30 minutes of intravitreal injection with vascular endothelial growth factor (VEGF) inhibitors, including brolucizumab (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Pagenax while the intraocular pressure is ≥30 mmHg). 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 Pagenax 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 and DME 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 (23mg) per dose, that is to say essentially "sodium-free".

Populations with limited data

There is limited experience with Pagenax treatment in diabetic patients with HbA1c greater than 10% or with proliferative diabetic retinopathy. There is also no experience of treatment with Pagenax in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with brolucizumab and for at least one month after the last dose when stopping treatment with brolucizumab.

Pregnancy

There are no or limited amount of data from the use of brolucizumab in pregnant women. A study in pregnant cynomolgus monkeys did not indicate any harmful effects with respect to reproductive toxicity. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Although the systemic exposure after ocular administration is very low due to its mechanism of action, there is a potential risk to embryofoetal development. Therefore, brolucizumab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breast-feeding

It is unknown whether brolucizumab is excreted in human milk. In a reproductive toxicity study, brolucizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys (see section 5.3). A risk to the breast-fed newborn/infant cannot be excluded. Brolucizumab is not recommended during breast-feeding and breast-feeding should not be started for at least one month after the last dose when stopping treatment with brolucizumab. 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.

Fertility

No reproductive or fertility studies have been conducted. VEGF inhibition has been shown to affect follicular development, corpus luteum function and fertility. Based on the mechanism of action of VEGF inhibitiors, there is a potential risk for female reproduction.

4.7 Effects on ability to drive and use machines

Pagenax has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances following the intravitreal injection and the associated eye examination. Patients should not drive or use machines until visual function has recovered sufficiently.

4.8 Undesirable effects

Summary of the safety profile

Wet AMD

For wet AMD, a total of 1,088 patients treated with brolucizumab constituted the safety population in two Phase III studies. Of these, 730 patients were treated with the recommended dose of 6mg.
The most frequently reported adverse reactions were reduced visual acuity (7.3%), cataract (7.0%), conjunctival haemorrhage (6.3%) and vitreous floaters (5.1%).
The most serious adverse reactions were blindness (0.8%), endophthalmitis (0.7%), retinal artery occlusion (0.8%) and retinal detachment (0.7%).

DME

For DME, a total of 558 patients treated with brolucizumab constituted the safety population in two Phase III studies. Of these, 368 patients were treated with the recommended dose of 6mg.
The most frequently reported adverse reaction was conjunctival haemorrhage (5.7%).
The most serious adverse reactions were retinal artery occlusion (0.5%) and endophthalmitis (0.3%).

Tabulated list of adverse reactions

The adverse reactions experienced following administration of Pagenax 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 and post-marketing experience

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
Iritis	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

Iridocyclitis	Uncommon
Anterior chamber flare	Uncommon
Corneal oedema	Uncommon
Vitreous haemorrhage	Uncommon
Retinal vascular occlusion	Uncommon
Retinal vasculitis	Uncommon

Description of selected adverse reactions

Immunogenicity

There is a potential for an immune response in patients treated with Pagenax.

Wet AMD

After dosing with Pagenax for 88 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 23–25% of patients.

DME

After dosing with Pagenax for 52 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 12-18% of patients.

Among AMD and DME patients with treatment-emergent antibodies, a higher number of intraocular inflammation adverse reactions were observed. After investigation, retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, were found to be immune-mediated adverse events related to exposure to Pagenax (see section 4.4). Anti-brolucizumab antibodies were not associated with an impact on clinical efficacy.

Product-class-related adverse reactions

There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the brolucizumab clinical studies in patients with AMD and DME. There were no major notable differences between the groups treated with brolucizumab and comparator.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 9.7 Antineoplastic and Immunosuppressive Medicines (Others)

Mechanism of action

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

Increased levels of signalling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathological ocular angiogenesis and retinal oedema. Brolucizumab binds with high 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, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability.

Pharmacodynamic effects

Wet AMD

In the HAWK and HARRIER studies, anatomical parameters related to leakage of blood and fluid that characterise choroidal neovascularisation (CNV) 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 Pagenax as early as 4 weeks after treatment initiation and up to week 48 and week 96.

At week 16, the reduction in CST was statistically significant on Pagenax versus aflibercept in both studies (HAWK: -161 vs. -134 microns; HARRIER: -174 vs. -134 microns). This decrease from baseline in CST was also statistically significant at week 48 (HAWK: -173 vs. -144 microns; HARRIER: -194 vs. -144 microns), and maintained to the end of each study at week 96 (HAWK: -175 vs. -149 microns; HARRIER: -198 vs. -155 microns).

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

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

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

DME

In the KESTREL and KITE studies, related anatomical parameters were part of the disease activity assessments guiding treatment decisions. Reductions in CST and in presence of IRF/SRF were observed in patients treated with Pagenax as early as 4 weeks after treatment initiation and up to week 52.

Clinical efficacy and safety

Wet AMD

The efficacy and safety of Pagenax 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 Pagenax and 729 on comparator aflibercept). Patient ages ranged from 50 to 97 years, with a mean age of 76 years.

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 comparator aflibercept was administered every 8 weeks after the first 3 monthly doses.

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 Pagenax versus aflibercept. In both studies, Pagenax (administered in an every 12 weeks or an every 8 weeks regimen) demonstrated non-inferior efficacy to aflibercept 2mg (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**	**Pagenax (n=360)**	**Aflibercept 2mg (n=360)**	**Difference (95% CI) brolucizumab – aflibercept**	**Pagenax (n=370)**	**Aflibercept 2mg (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)
% 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

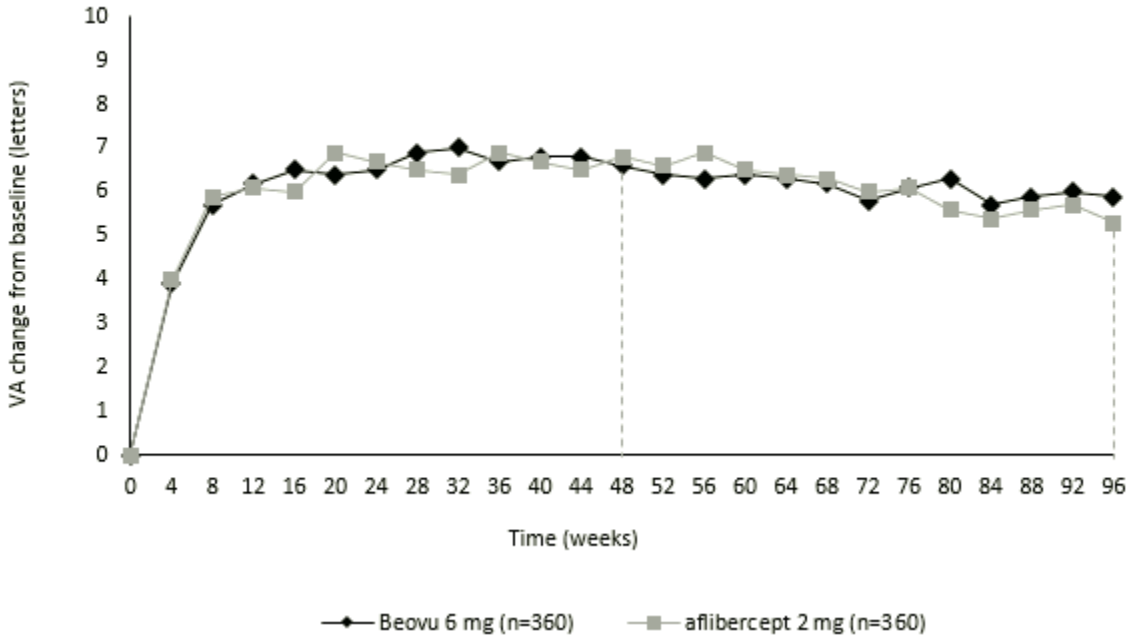
SE: standard error

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

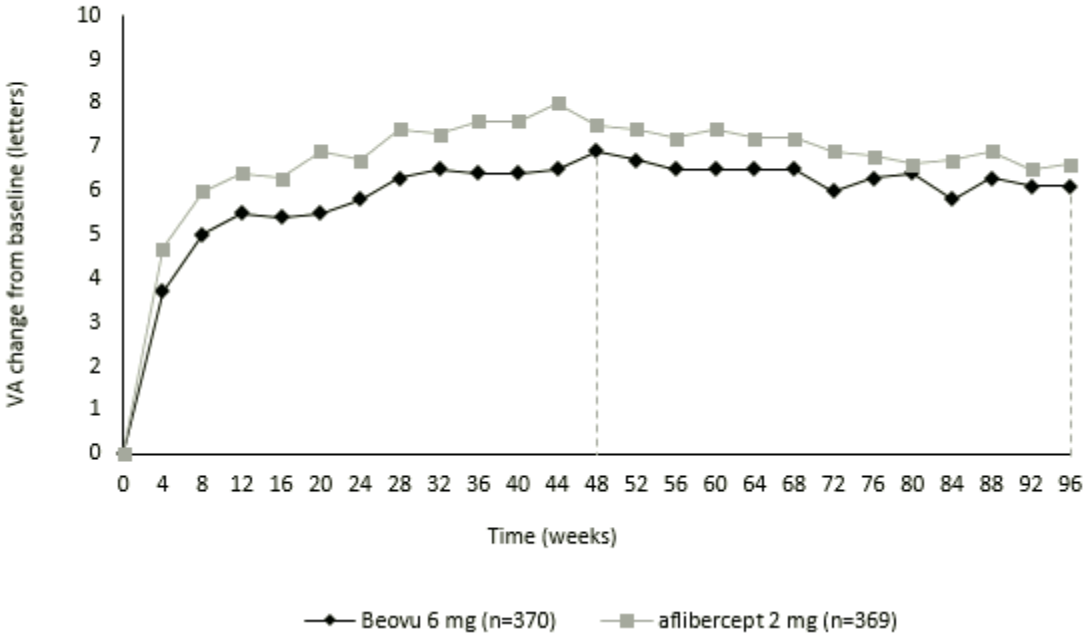
[b)] Key secondary endpoint, accounting for differences in timing of Pagenax and aflibercept treatments.

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 Pagenax 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

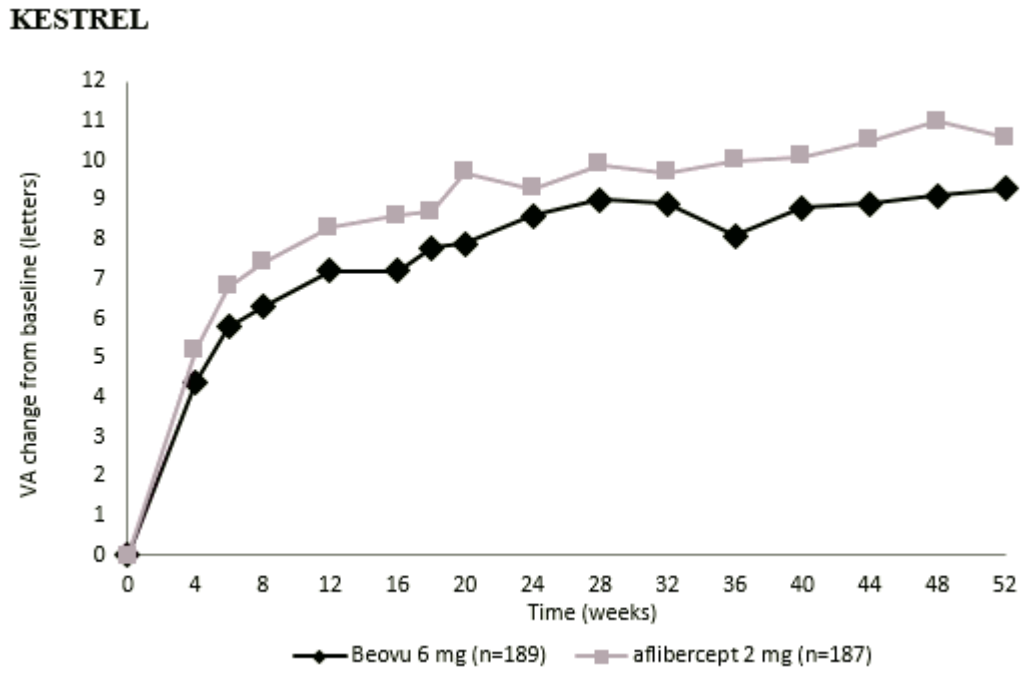
week 48. Of patients on the 12-weekly interval at week 48, 82% and 75% remained on the 12-weekly dosing interval up to week 96.
Treatment effects in evaluable subgroups (e.g. age, gender, race, baseline visual acuity, baseline retinal thickness, lesion type, lesion size, fluid status) in each study were 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. Disease activity was assessed throughout the studies. Anatomical parameters of disease activity were decreased at week 48 and at week 96 for Pagenax compared to aflibercept (see "Pharmacodynamic effects").
The percentage difference in patients with disease activity at week 16 was statistically significant on Pagenax versus aflibercept (24% vs 35% in HAWK, p=0.0013; 23% vs 32% in HARRIER, p=0.0021).
In both studies, Pagenax 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 Pagenax 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).
DME
The efficacy and safety of Pagenax were assessed in two randomised, multicentre, double-masked, active-controlled Phase III studies (KESTREL and KITE) in patients with visual impairment due to diabetic macular oedema. A total of 926 patients were treated in these studies for one year (558 on brolucizumab and 368 on aflibercept 2mg). Patient ages ranged from 23 to 87 years, with a mean age of 63 years.
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 CST) at any of these visits were adjusted to an every 8 weeks treatment interval. The comparator aflibercept was administered every 8 weeks after the first 5 monthly doses.
Results
The primary efficacy endpoint for the studies was the change from baseline in BCVA to week 52, as measured by the ETDRS letter score, with the primary objective being to demonstrate non-inferiority of Pagenax versus aflibercept 2mg. In both studies, Pagenax (administered in an every 12 weeks or an every 8 weeks regimen) demonstrated non-inferior efficacy to aflibercept 2mg (administered every 8 weeks).
The results of KESTREL and KITE also demonstrated non-inferiority of Pagenax versus aflibercept 2mg for the key secondary endpoint (average change from baseline in BVCA over the period week 40 to week 52).
Detailed results of both studies are shown in Table 3 and in Figure 2 below.

Table 3 Visual acuity outcomes at week 52 in Phase III - KESTREL and KITE studies

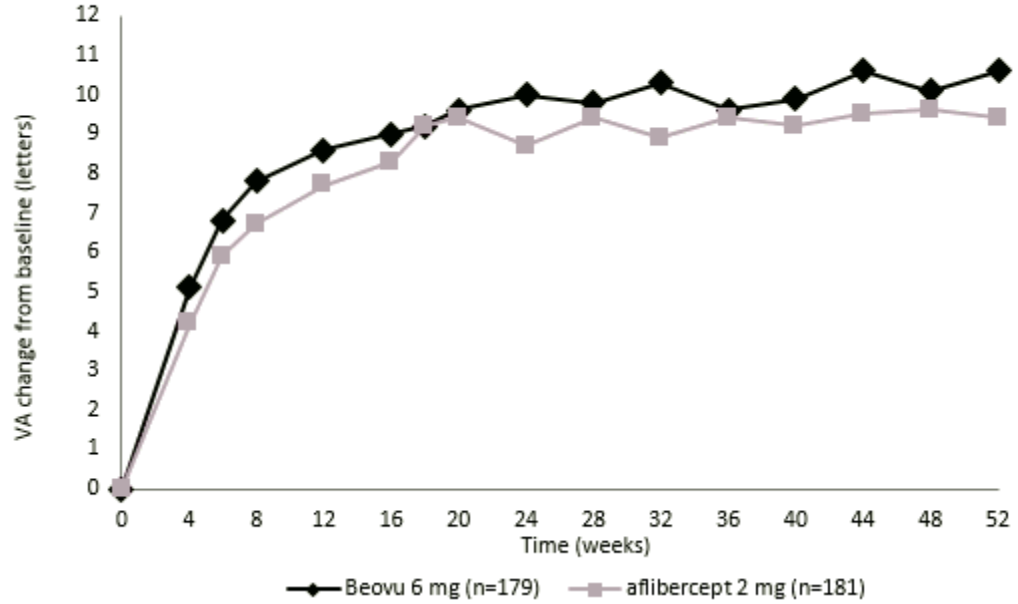
		KESTREL			KITE		
Efficacy outcome	**Week**	**Pagenax (n=189)**	**Aflibercept 2mg (n=187)**	**Difference (95% CI) brolucizumab – aflibercept**	**Pagenax (n=179)**	**Aflibercept 2mg (n=181)**	**Difference (95% CI) brolucizumab–aflibercept**
Change from baseline in BCVA (measured by ETDRS letters score) – 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]
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)

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.
ETDRS: early treatment diabetic retinopathy study
LS: least-square
SE: standard error
[a] P-value referring to the non-inferiority hypothesis with a non-inferiority margin of 4.0 letters

Figure 2 Mean change in visual acuity from baseline to week 52 in KESTREL and KITE studies



KITE



These visual acuity gains were achieved with 55% and 50% of patients treated with Pagenax on a 12-weekly dosing interval at week 52 in KESTREL and KITE, respectively. Among patients identified as eligible for the 12-weekly regimen during the first 12-week interval, 88% and 95% remained on the 12-weekly interval at week 52.

Treatment effects in evaluable subgroups (e.g. 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 populations.

Disease activity was assessed by changes in visual acuity and/or anatomical parameters, including CST and/or presence of IRF/SRF. Disease activity was assessed throughout the studies.

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, Pagenax showed non-inferiority to aflibercept 2mg in the proportion of subjects with at least a 2-step improvement from baseline in DRSS at week 52, using a non-inferiority margin of 10%. Estimated proportions were 28.9% and 24.9% in Pagenax and aflibercept 2mg, respectively, resulting in a treatment difference of 4.0% (95% CI: [-0.6, 8.6]).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Pagenax in all subsets of the paediatric population in neovascular AMD and DME (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption and distribution

After intravitreal administration of 6mg brolucizumab per eye to patients with nAMD, the geometirc 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.

Biotransformation and elimination

Brolucizumab is a monoclonal antibody fragment and no metabolism studies have been conducted. As a single-chain antibody fragment, free brolucizumab is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF, passive renal elimination and metabolism via proteolysis.
After intravitreal injections, brolucizumab was eliminated with an apparent systemic half-life of 4.4 days. Concentrations were generally near or below the quantitation limit (<0.5 ng/ml) approximately 4 weeks after dosing in most patients. Brolucizumab did not accumulate in the serum when administered intravitreally every 4 weeks.
Special populations
Elderly
There were no relevant differences in systemic pharmacokinetics following intravitreal injection in a study with 22 patients aged 65 to 74 years, 18 patients aged 75 to 84 years and 3 patients aged ≥85 years.
Renal impairment
The systemic pharmacokinetics of brolucizumab was evaluated in nAMD patients with normal renal function (≥90 ml/min [n=21]), with mild (60 to <90 ml/min [n=22]) or moderate (30 to <60 ml/min [n=7]) renal impairment. While the mean systemic clearance values for patients with mild or moderate renal impairment were generally lower than patients with normal renal function, no significant impact of mild and moderate renal impairment on the overall systemic exposure to brolucizumab was observed. 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
No studies have been conducted on the carcinogenic or mutagenic potential of brolucizumab.
In pregnant cynomolgus monkeys, brolucizumab was administered once every 4 weeks by intravitreal injection at dose levels resulting in maximal systemic exposures 6-fold higher than those in humans at the maximum recommended dose (based on serum C_{max}). There was no impact on embryofoetal development, pregnancy or parturition, or on the survival, growth or postnatal development of offspring. Nevertheless, based on its pharmacological effect, brolucizumab should be regarded as potentially teratogenic and embryo-foetotoxic.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium citrate
Sucrose
Polysorbate 80
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

24 months

6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C).
Do not freeze.

6.5 Nature and contents of container
0.23 ml sterile solution in a colorless 2 ml glass vial with a grey ETFE-coated rubber stopper and an aluminum seal with violet polypropylene flip-off cap.

6.6 Special precautions for disposal and other handling
The solution should be inspected visually upon removal from the refrigerator and prior to administration. If particulates or cloudiness are visible, it must not be used and appropriate replacement procedures followed.
Do not use if the packaging, or vial are damaged or expired. Detailed instructions for use are provided in the package leaflet.
Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

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