WARNING: To be sold by retail on the prescription of an Ophthalmologist only.

Brolucizumab solution for injection 120 mg/ml

PAGENAX®

COMPOSITION

Active substances

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

Excipients

2.58 mg/ml sodium citrate, 58 mg/ml sucrose, 0.2 mg/ml polysorbate 80, sodium hydroxide (for pH adjustment to approx. 7.2) and water for injections.

PHARMACEUTICAL FORM AND QUANTITY OF ACTIVE SUBSTANCE PER UNIT

Vial

Each vial contains 27.6 mg brolucizumab in 0.23 ml of solution. This amount is sufficient to administer a single dose of 0.05 ml, containing 6 mg brolucizumab. 1 ml of solution for intravitreal injection contains 120 mg brolucizumab.

INDICATIONS/POTENTIAL USES

Pagenax is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME).

DOSAGE/ADMINISTRATION

Single-use vial. For intravitreal use only. Each vial may only be used for the treatment of a single eye.

Pagenax must be administered by a qualified physician.

Usual dosage

Neovascular (wet) age-related macular degeneration (AMD)

The recommended dose for Pagenax is 6 mg (0.05 mL) administered as an intravitreal injection, with the first three injections taking place at 4-week intervals (monthly). Thereafter, Pagenax is administered every 12 weeks (3 months). The physician may individually define treatment intervals based on disease activity as measured by visual acuity and/or anatomical parameters. The treatment interval may be adjusted to every 8 weeks (2 months) (see “Properties/Actions”); however, it should not be less than every 8 weeks (2 months) (see “Warnings and precautions”).

Diabetic macular edema (DME)

The recommended dose for Pagenax is 6 mg (0.05 mL) administered by intravitreal injection, with the first five injections taking place at 6-week intervals. Thereafter, Pagenax is administered every 12 weeks (3 months). The physician may individually define treatment intervals based on disease activity as measured by visual acuity and/or anatomical parameters. In patients with disease activity, treatment every 8 weeks (2 months) may be considered (see “Properties/Actions”); however, the treatment interval should not be less than every 8 weeks (2 months) (see “Warnings and precautions”).

To ensure traceability of medicinal products produced using biotechnology, it is recommended that the trade name and batch number be documented at every treatment.

Special dosage instructions

Patients with hepatic impairment
No studies have been performed in patients with hepatic impairment.

Patients with renal impairment

No dose adjustment is recommended in patients with renal impairment. There are only limited data available in patients with moderate renal impairment and no data in patients with severe renal impairment (see “Properties/Actions”).

Elderly patients
No dose adjustment is required in patients aged 65 years or above.

Children and adolescents
The safety and efficacy of Pagenax in children and adolescents have not been established.

Method of administration
As with all medicinal products for intravitreal use, Pagenax should be inspected visually prior to administration (see “Instructions for use and handling”).

The intravitreal injection must be carried out under aseptic conditions. This includes surgical hand disinfection, sterile surgical gloves, a sterile drape and a sterile eyelid speculum (or similar instrument). Sterile paracentesis equipment should be available as a precautionary measure. The patient’s medical history should be thoroughly evaluated for possible hypersensitivity reactions prior to the intravitreal injection (see “Contraindications”). Adequate anaesthesia and a broad-spectrum topical antiseptic to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

For information on the preparation of Pagenax, see Instructions for use and handling (see “Other information”).

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 can then be injected slowly. Subsequent injections must be performed at different scleral sites.

The safety and efficacy of Pagenax treatment in both eyes concurrently have not been studied.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or any of the excipients.
- Existing or suspected ocular or periocular infection.
- Existing intraocular inflammation.

WARNINGS AND PRECAUTIONS

Intravitreal injection-related reactions

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

Intravitreal injections, including those with Pagenax, have been associated with endophthalmitis, intraocular inflammation and retinal detachment.

Cases of retinal vasculitis and/or retinal vascular occlusion have been reported in patients treated with Pagenax. Treatment with Pagenax must be discontinued in affected patients. The described cases of retinal vasculitis/retinal vascular occlusion are immune-mediated adverse events and may occur after the first intravitreal injection. These events are generally associated with intraocular inflammation (i.e. intraocular inflammation represents a possible risk factor for these adverse effects). To reduce the risk of retinal vasculitis and/or retinal vascular occlusion, patients who develop intraocular inflammation during treatment with Pagenax must be carefully monitored. In addition, the incidence of intraocular inflammation was investigated based on anti-brolucizumab antibody (ADA) status before and during treatment with Pagenax. The corresponding analysis of data from the phase III studies (HAWK and HARRIER) showed that patients with an immune response to Pagenax (induction or boost of ADAs) had a risk of developing intraocular inflammation that was multiple times higher than in patients without an immune response (see "Contraindications" and "Adverse effects").

Pagenax must be always administered under aseptic injection conditions. Patients should be instructed to report possible symptoms of any of the above-mentioned events without delay.

In a phase IIIa clinical study (MERLIN) patients with nAMD who received Pagenax every 4 weeks as a maintenance dose experienced a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion than patients who received Pagenax every 8 or 12 weeks as a maintenance dose in the pivotal phase III clinical studies (HAWK and HARRIER). The interval between 2 Pagenax doses during maintenance treatment should not be less than 8 weeks (see "Dosage/Administration").

Intraocular pressure increases

Transient increases in intraocular pressure have been seen within the first 30 minutes of injection, similar to those observed with intravitreal administration of other VEGF inhibitors (see "Adverse effects"). Sustained intraocular pressure increases have also been reported. Particular caution is required 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 as necessary.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with brolucizumab (see "Adverse effects"). Patients should be instructed to inform their physician if they develop symptoms such as eye pain or increased eye discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision or increased sensitivity to light (see "Adverse effects").

Withholding treatment

In intravitreal anti-VEGF treatments, treatment should be withheld and not resumed earlier than the next scheduled treatment in the following cases:

- a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity
- a retinal tear
- a subretinal haemorrhage involving the centre of the fovea or if the size of the haemorrhage is ≥50% of the total affected lesion
- performed or planned intraocular surgery within the previous or next 28 days.

Retinal pigment epithelial tear

Large-scale and/or severe pigment epithelial retinal detachment represent risk factors for the development of a retinal pigment epithelial tear after anti-VEGF therapy in patients with wet AMD. When initiating brolucizumab therapy, caution is required in patients with these risk factors for retinal pigment epithelial tears.

Rhegmatogenous retinal detachment or macular holes

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

Systemic effects following intravitreal use

Systemic adverse effects, including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. There is a theoretical risk that these may relate to VEGF inhibition. There are only limited safety data on the treatment of AMD and DME patients with a history of stroke, transient ischaemic attacks or myocardial infarction within the last 3 months. Caution should be exercised when treating such patients.

INTERACTIONS

No formal interaction studies have been performed.

PREGNANCY/BREAST-FEEDING

Women of childbearing potential

Women of childbearing potential must use a reliable method of contraception during treatment with Pagenax and for at least one month after stopping treatment with Pagenax.

Pregnancy

There are no adequate and well-controlled studies of Pagenax administration in pregnant women. The potential risk of use of Pagenax in pregnancy is unknown. Animal studies showed no evidence of reproductive toxicity (“see Preclinical data”). However, based on the anti-VEGF mechanism of action brolucizumab must be regarded as potentially teratogenic and embryo-/fetotoxic. Therefore, Pagenax must not be administered during pregnancy unless absolutely necessary.

Breast-feeding
It is unknown if brolucizumab is transferred into human milk after administration of Pagenax. There are no data on the effects of Pagenax on the breast-fed infant or milk production. Because of the potential for adverse drug reactions in breast-fed infants, breast-feeding is not recommended during treatment and for at least one month after stopping treatment with Pagenax.

Fertility
No relevant data are available.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients may experience temporary visual impairment after an intravitreal injection with Pagenax and the associated eye examination. Patients must therefore be advised not to drive or use machines until visual function has recovered sufficiently.

ADVERSE EFFECTS

Patients with wet AMD

A total of 1,088 patients treated with Pagenax constituted the safety population in the two phase III studies HAWK and HARRIER. The cumulative exposure to Pagenax was 96 weeks and 730 patients were treated with the recommended dose of 6 mg.

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

Less common serious adverse drug reactions reported in less than 1% of patients treated with 6 mg Pagenax were endophthalmitis, blindness, retinal artery occlusion and retinal detachment.

Patients with DME

The safety of Pagenax was studied in two active-controlled phase III studies (KESTREL and KITE) each conducted in 368 patients with visual impairment due to DME treated with the recommended dose of 6 mg brolucizumab for 52 weeks.

The ocular and non-ocular events in the KESTREL and KITE studies were reported with a similar frequency and severity to those seen in the nAMD studies. Retinal vascular occlusion was reported in two patients (0.5%) treated with Pagenax and one patient (0.3%) treated with 2 mg aflibercept. Retinal vasculitis was reported in one patient (0.3%) treated with Pagenax and no patients treated with 2 mg aflibercept.

Adverse drug reactions from the HAWK and HARRIER clinical studies are listed by frequency, with the most frequent adverse drug reactions listed first. 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).

Immune system disorders
Common: Hypersensitivity[a]

Eye disorders
Common: Reduced visual acuity, cataract, conjunctival haemorrhage, vitreous floaters, eye pain, retinal haemorrhage, vitreous detachment, increased intraocular pressure, conjunctivitis, retinal pigment epithelial tear, blurred vision, uveitis, corneal abrasion, punctate keratitis, iritis, retinal tear.
Uncommon: Conjunctival hyperaemia, increased lacrimation, blindness, retinal artery occlusion, abnormal sensation in eye, endophthalmitis, retinal detachment, detachment of retinal pigment epithelium, vitritis,

anterior chamber inflammation, iridocyclitis, anterior chamber flare, corneal oedema, vitreous haemorrhage.

a) Including urticaria, rash, pruritus, erythema.

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

The following adverse drug reactions are from spontaneous reports and literature cases associated with post-marketing experience with Pagenax. Because these effects are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequencies. Therefore, these adverse drug reactions have been assigned the frequency category “not known”. Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class adverse drug reactions are listed in order of decreasing seriousness.

Eye disorders
Not known: Retinal vascular occlusion, retinal vasculitis

Intraocular inflammation

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

Post-marketing safety data indicate a risk of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion, during Pagenax treatment. To identify potential risk factors, real-world data from nAMD patients treated for up to 6 months were analysed retrospectively. The results of this analysis indicate an increased risk of the above-mentioned events in patients who have experienced intraocular inflammation and/or retinal vascular occlusion in the year prior to the start of Pagenax treatment.

Immunogenicity
As with all therapeutic proteins, there is also a potential risk of an immune response in patients treated with Pagenax. The immunogenicity of Pagenax was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Pagenax 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 Pagenax with the incidence of antibodies to other products may be misleading. Antibodies, including single-chain antibodies, to a variety of therapeutic proteins produced using biotechnology have been detected in treatment-naïve patients before the start of treatment.

Wet AMD

The pre-treatment incidence of anti-brolucizumab antibodies was 35-52%. After administration of Pagenax for a period of 88 weeks treatment-emergent anti-brolucizumab antibodies were detected in 23-25% of patients.

Diabetic macular edema (DME)

The pre-treatment incidence of anti-brolucizumab antibodies was 64%. After dosing with Pagenax for 52 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 12 to 18% 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 Pagenax. This treatment-emergent antibody response may occur after the first intravitreal injection (see “Warnings and precautions”).

Product class-related adverse effects

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. There were no major differences between the groups treated with brolucizumab and the comparator.

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via appropriate systems.

OVERDOSE

An overdose with more than the 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, treated.

Properties/Actions

ATC code
S01LA06

Mechanism of action

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

Pharmacodynamics
Wet AMD

In the HAWK and HARRIER studies, related anatomical parameters were part of the disease activity assessments forming the basis of treatment decisions. Reductions in central subfield thickness (CST) and in the presence of intraretinal/subretinal fluid (IRF/SRF) or subretinal 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.

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

Diabetic macular edema (DME)

In the KESTREL and KITE studies relevant anatomical parameters were part of the disease activity assessment guiding treatment decisions. Reductions in central subfield thickness (CST) and in presence of intraretinal/subretinal fluid (IRF/SRF) were observed in patients treated with Pagenax as early as 4 weeks after treatment initiation and up to week 52.

Clinical efficacy

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

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

1) 3 mg brolucizumab administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses.
2) 6 mg brolucizumab administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses.
3) 2 mg aflibercept administered every 8 weeks (q8w) after the first 3 monthly doses.

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

1) 6 mg brolucizumab administered every 12 or 8 weeks (q12w/q8w) after the first 3 monthly doses.
2) 2 mg aflibercept administered every 8 weeks (q8w) after the first 3 monthly doses.

In both studies, after the first 3 monthly doses (week 0, 4 and 8), brolucizumab patients were treated every 12 weeks with the option of switching to an 8-week treatment interval 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 central subfield thickness (CST) or presence of retinal fluids (IRF/SRF, sub-RPE)) at any of these visits were switched to an 8-week treatment interval.

Results

The primary efficacy endpoint for the studies was the change from baseline in best corrected visual acuity (BCVA) at week 48 as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter charts, with the primary objective being to demonstrate non-inferiority of Pagenax versus aflibercept. In both studies Pagenax (administered in a 12-/8-week regimen) demonstrated non-inferior efficacy to 2 mg aflibercept administered every 8 weeks.

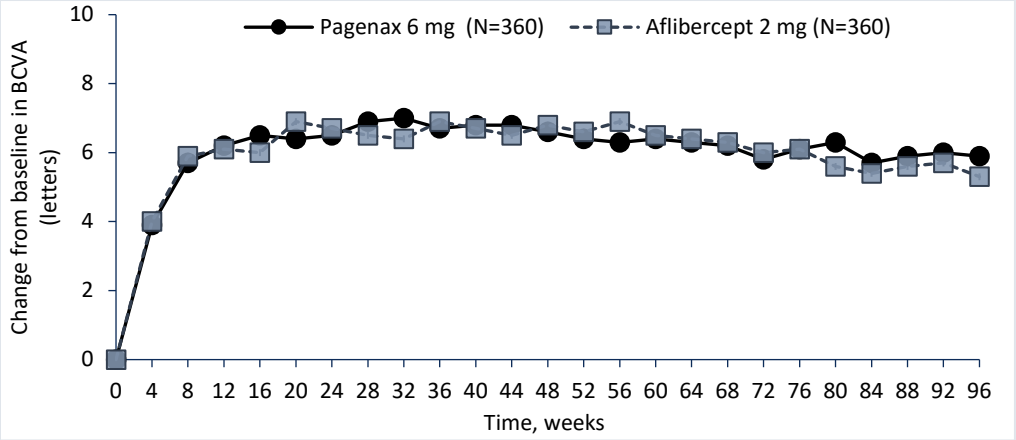
In the HAWK study, at week 48 patients achieved a mean change from baseline of +6.6 letters and +6.8 letters ($p<0.0001$) in the 6 mg Pagenax and aflibercept groups, respectively. The mean change from baseline in the 3 mg Pagenax group was +6.1 letters ($p=0.0003$). The proportion of patients who achieved a gain in visual acuity of at least 15 letters from baseline was 33.6% in the brolucizumab group versus 25.4% in the aflibercept group. The proportion of patients who lost 15 letters or more of visual acuity from baseline was 6.4% in the 6 mg brolucizumab group versus 5.5% in the aflibercept group.

In the HARRIER study, at week 48 patients achieved a mean change from baseline of +6.9 letters and +7.6 letters ($p<0.0001$) in the Pagenax and aflibercept groups, respectively. The proportion of patients who achieved a gain in visual acuity of at least 15 letters from baseline was 29.3% in the brolucizumab group versus 29.9% in the aflibercept group. The proportion of patients who lost 15 letters or more of visual acuity from baseline was 3.8% in the 6 mg brolucizumab group versus 4.8% in the aflibercept group.

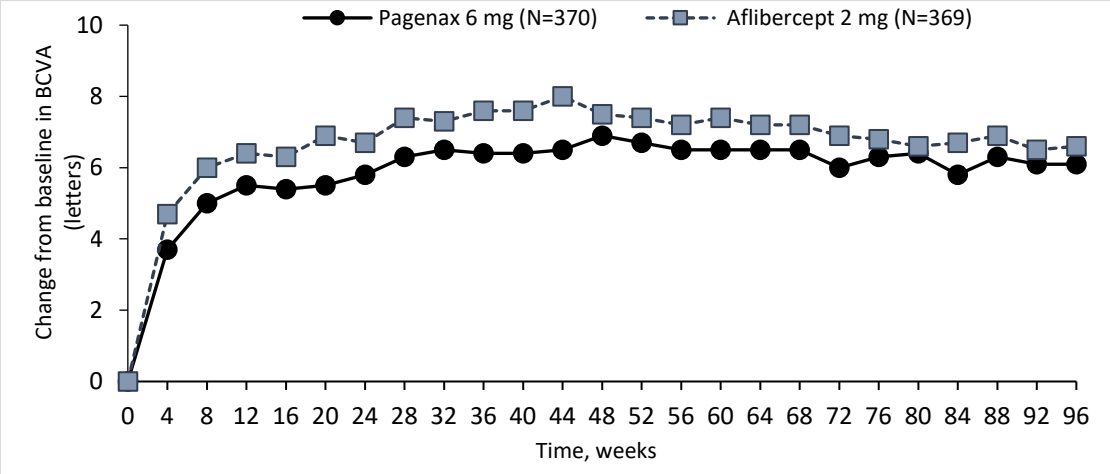
The visual acuity gains observed in the first year were maintained in the second year.

Figure1 **Mean change in visual acuity from baseline to week 96 in HAWK and HARRIER studies**

HAWK



HARRIER



In the HAWK and HARRIER studies 56% and 51% of patients, respectively, treated with Pagenax at a 12-week treatment interval achieved these visual acuity gains (mean change from baseline) at week 48 and 45% and 39% of patients, respectively, did so at week 96.

Among patients who, during the first 12-week treatment interval, had been identified as suitable for this treatment interval, the 12-week treatment interval was continued up to week 48 in 85% and 82% of patients, respectively. In 82% and 75% of patients, respectively, who had been treated on the basis of the 12-week treatment interval at week 48 the 12-week treatment interval was maintained from week 48 to week 96.

Treatment effects in evaluable subgroups (e.g. age, gender, ethnicity, baseline visual acuity, baseline retinal thickness, lesion type, lesion size, fluid status) in both studies were largely consistent with the results in the overall population.

Disease activity was assessed by changes in visual acuity and/or morphological criteria, including central subfield thickness (CST) and presence of retinal fluids (IRF/SRF, sub-RPE). At week 16, when disease activity was first assessed to determine the treatment interval, statistically fewer patients treated with Pagenax showed disease activity compared to patients treated with 2 mg aflibercept (24% vs 35% in HAWK, p=0.0013; 23% vs 32% in HARRIER, p=0.0021). Disease activity was assessed throughout the studies. Morphological criteria of disease activity were decreased at week 48 and at week 96 in the Pagenax group compared to aflibercept (Table 1).

Table 1 Disease activity evaluation in HAWK and HARRIER studies up to week 96

		HAWK			**HARRIER**		
Efficacy outcome (pre-specified secondary endpoints)	**At week**	**Pagenax (N=360)**	**2mg Aflibercept (N=360)**	**Difference (95% CI) brolucizumab and aflibercept**	**Pagenax (N=360)**	**2 mg Aflibercept (N=369)**	**Difference (95% CI) brolucizumab and aflibercept**
Mean change in CST from baseline (µm)	16 [c)]	-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)]

CST: central subfield thickness; IRF/SRF: intraretinal/subretinal fluid; RPE: retinal pigment epithelium

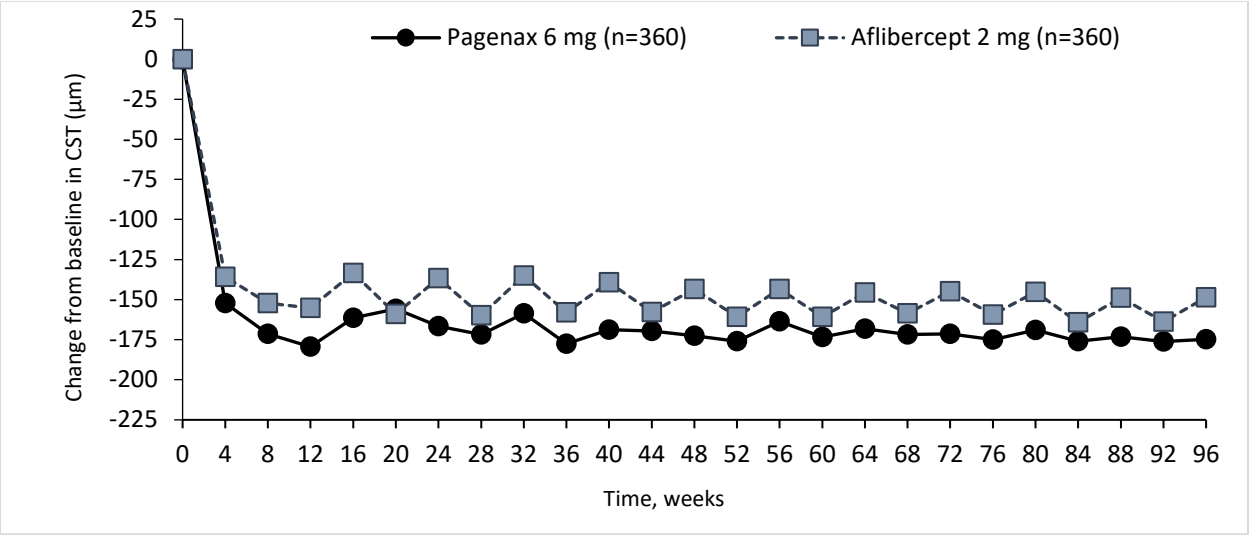
[a)] Secondary endpoint in HARRIER, confirmatory analysis in HAWK. 1-sided p-values for superiority of brolucizumab

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

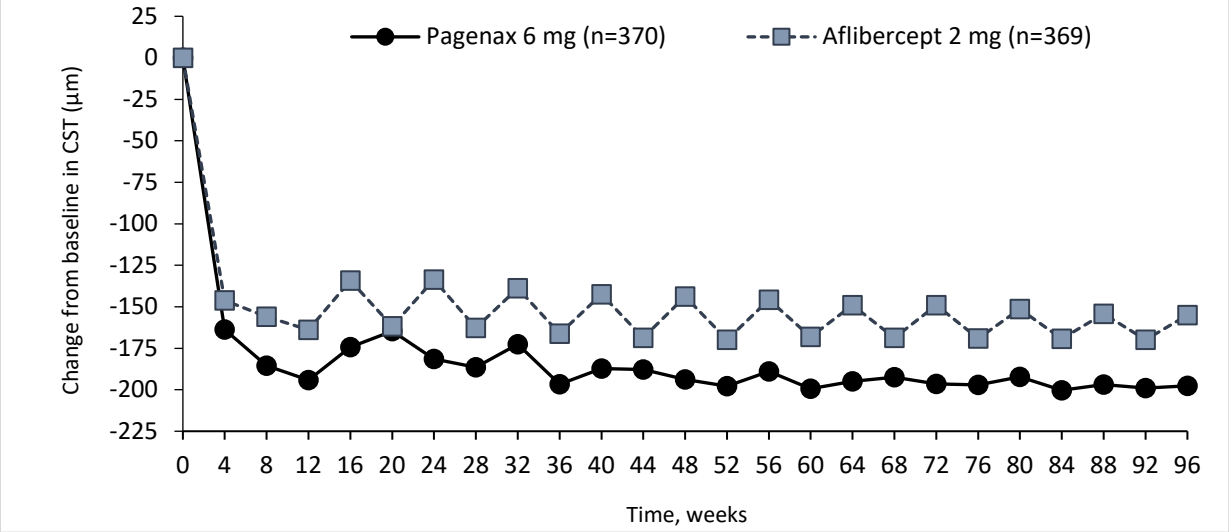
[c)] Up to week 16 treatment exposure was identical, allowing a matched comparison of Pagenax and aflibercept.

Figure 2 **Central subfield thickness change from baseline to week 96 in HAWK and HARRIER studies**

HAWK



HARRIER



In both studies, treatment with Pagenax led to clinically meaningful changes from baseline in the pre-specified secondary efficacy endpoint of patient-reported outcomes, recorded using US National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, corresponding to a 15-letter gain in best corrected visual acuity (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 vision, distance

vision, social functioning, mental health, difficulties in performing social roles, dependency on others, driving, colour vision and peripheral vision).

Treatment of DME

The safety and efficacy of Pagenax were assessed in two randomised, multicentre, double-blind, 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 1 year (558 with brolucizumab and 368 with 2 mg aflibercept). Patient ages ranged from 23 to 87 years, with a mean age of 63 years.

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

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

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

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

In both studies, after the first five doses (at weeks 0, 6, 12, 18 and 24), patients were treated with brolucizumab every 12 weeks with the option of switching to an 8-week treatment interval based on disease activity. Disease activity was assessed by a physician during the first 12-week treatment interval (at weeks 32 and 36) and at each subsequent scheduled 12-weekly treatment visit. Patients who showed disease activity (e.g. decreased visual acuity, increased central subfield thickness (CST)) at any of these visits were switched to an 8-week 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 in best corrected visual acuity (BCVA) at week 52 as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter charts, with the primary objective being to demonstrate non-inferiority of Pagenax versus 2 mg aflibercept. In both studies Pagenax (administered in a 12-/8-week regimen) demonstrated non-inferior efficacy to 2 mg aflibercept administered every 8 weeks.

The results of the KESTREL and KITE studies also demonstrated non-inferiority of Pagenax versus 2 mg aflibercept for the key secondary endpoint (average change from baseline in visual acuity over the period from week 40 to week 52).

The median number of injections given over 12 months was 7 in patients treated with Pagenax versus 9 in patients treated with 2 mg aflibercept.

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

Table 2 Efficacy outcomes at week 52 in the phase III - KESTREL and KITE studies

		KESTREL			KITE		
Efficacy outcome	**At week**	**Pagenax (n=189)**	**2 mg aflibercept (n=187)**	**Difference (95% CI) Pagenax – aflibercept**	**Pagenax (n=179)**	**2 mg aflibercept (n=181)**	**Difference (95% CI) Pagenax – aflibercept**
Change from baseline in BCVA measured using ETDRS letter charts – 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 of at least 84 letters (%)	52	36.0	40.1	-4.1 (-13.3, 5.9)	46.8	37.2	9.6 (-0.4, 20.2)
Mean change from baseline in CST (micrometres) – 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]
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)

BCVA: Best corrected visual acuity; BCVA assessments after the start of alternative DME treatment in the study eye were censored and replaced by the last value prior to the start of this alternative treatment

CST: Central subfield thickness

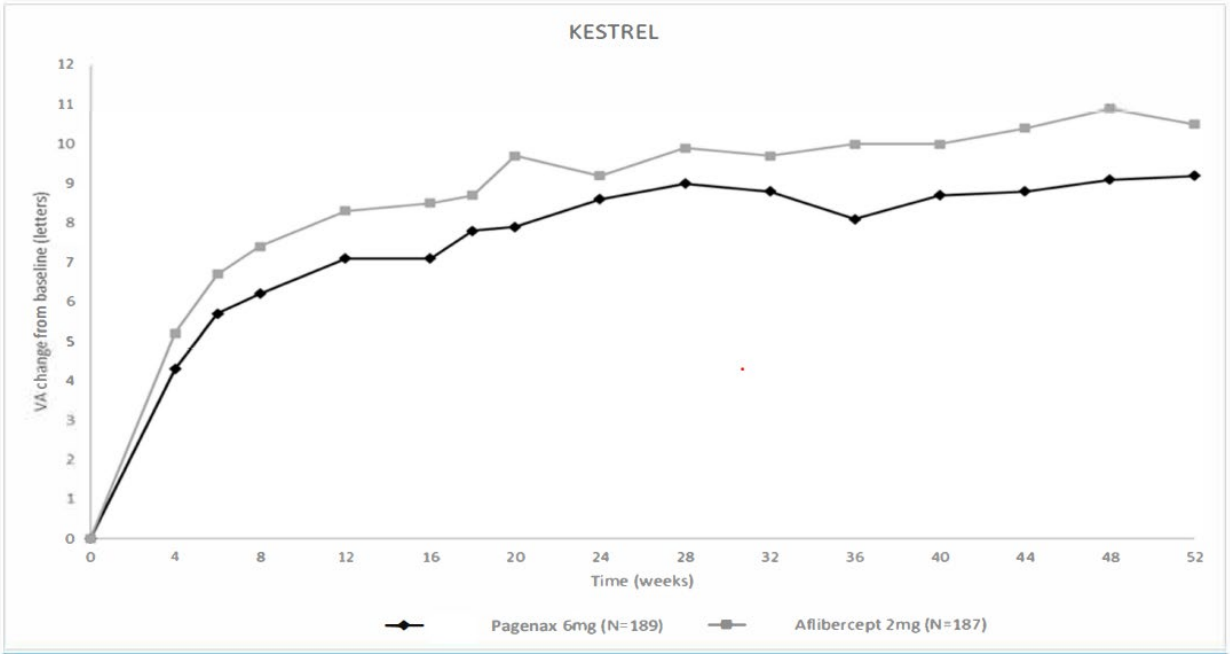
IRF: Intraretinal fluid; SRF: Subretinal fluid

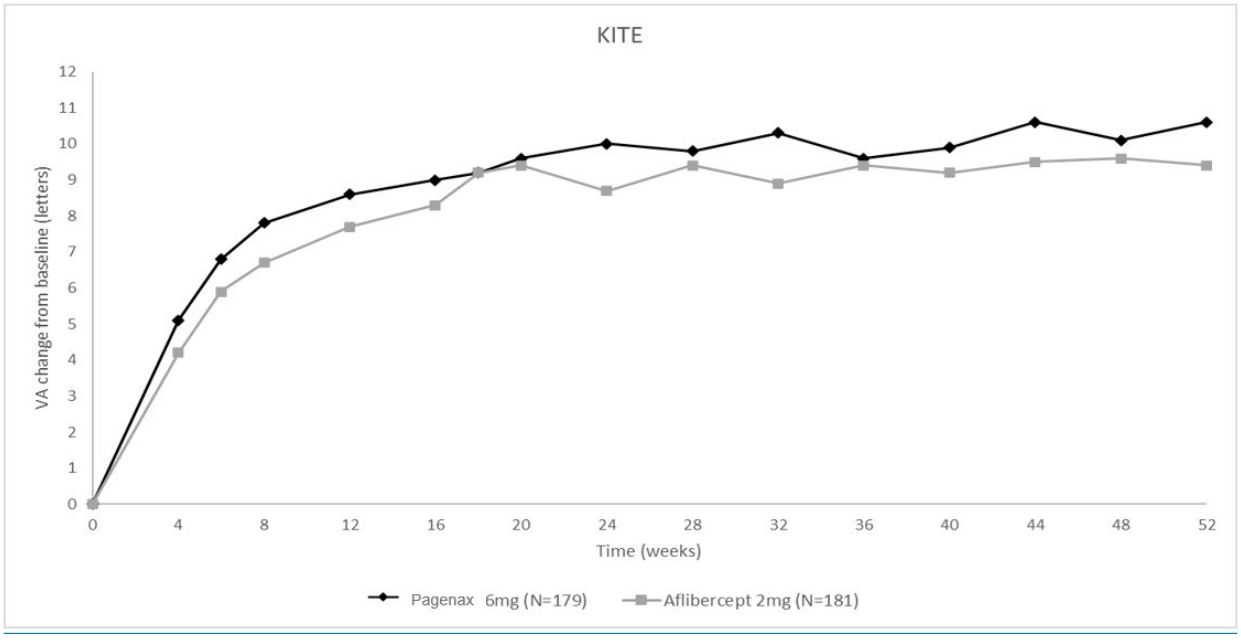
CST and fluid status assessments after the start of other DME treatment in the study eye were censored and replaced by the last value prior to the start of this other treatment

[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 3 Mean change in visual acuity from baseline to week 52 in KESTREL and KITE studies





In the KESTREL and KITE studies 55% and 50% of patients, respectively, treated with 6 mg Pagenax at a 12-week treatment interval achieved these visual acuity gains at week 52. Among patients who, during

the first 12-week treatment interval, had been identified as suitable for this treatment interval, the 12-week treatment interval was continued up to week 52 in 88% and 95% of patients, respectively.

Treatment effects in evaluable subgroups (e.g. age, gender, baseline HbA1c, baseline visual acuity, baseline retinal thickness, DME lesion type, duration of DME since diagnosis, retinal fluid status) in both studies were largely consistent with the results in the overall population.

In both studies treatment with Pagenax led to improvements from baseline in the pre-specified secondary efficacy endpoint of patient-reported outcomes, recorded using the US National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, corresponding to a 15-letter gain in best corrected visual acuity (BCVA).

No treatment differences were found between Pagenax and 2 mg aflibercept for other subscales of this questionnaire.

Diabetic Retinopathy Severity Score (DRSS) was determined in both the KESTREL and KITE studies. At baseline 98.1% of patients in both the KESTREL and KITE studies had a gradable Diabetic Retinopathy Severity Score. Based on the pooled analysis 28.9% of patients treated with Pagenax experienced an at least 2-step improvement from baseline to week 52 in DRSS score compared to 24.9% of patients treated with 2 mg aflibercept. The estimated difference between Pagenax and 2 mg aflibercept was 4.0% (95% CI: [-0.6, 8.6]).

PHARMACOKINETICS

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

Distribution
After intravitreal administration of 6 mg brolucizumab per eye to nAMD patients the mean C_{max} of free brolucizumab in the serum was 49.0 ng/ml (range: 8.97 to 548 ng/ml) and was attained within one day. Mean AUC was 6000 h*ng/ml (range: 1420-60400 h*ng/ml).

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

Elimination
After intravitreal injection brolucizumab was eliminated with an apparent systemic half-life of 4.4 days. Pagenax did not accumulate in the serum when administered intravitreally every 4 weeks.

Pharmacokinetics in special populations

Hepatic impairment

Pharmacokinetics have not been studied in patients with hepatic impairment.

Renal impairment
The systemic pharmacokinetics of brolucizumab were evaluated in nAMD patients for whom both serum brolucizumab pharmacokinetic data and brolucizumab creatinine clearance data were available. The geometric mean ratio (90% CI) in patients with mild (60 to <90 ml/min (n=22)) and moderate

(30 to <60 ml/min (n=3)) renal impairment compared to patients with normal renal function is 1.4 (0.7, 2.9) and 1.7 (1.0, 2.8), respectively, for brolucizumab C_{max} and the ratio for AUC_{inf} is 1.4 (0.7, 2.9) and 1.0 (0.5, 2.0), respectively. No patients with severe (<30 ml/min) renal impairment were studied.

Elderly patients
Data on the pharmacokinetics of brolucizumab in elderly patients are limited, so that it is not possible to draw conclusions regarding the effect of ageing on the pharmacokinetics of brolucizumab.

Genetic polymorphism
Ethnic groups

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

PRECLINICAL DATA

Long-term toxicity (repeated-dose toxicity)
Intravitreal injections of brolucizumab to cynomolgus monkeys at dosage strengths of up to 6 mg/eye every 4 weeks for 26 weeks resulted in no ocular or systemic effects and were well tolerated.

Mutagenicity/carcinogenicity
No studies have been conducted to assess the mutagenic or carcinogenic potential of Pagenax.

Reproductive toxicity

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 these animals 28 days post-partum, with blood and milk collected for toxicokinetic evaluations. The intravitreal administration of brolucizumab had no impact on embryo-fetal development, pregnancy or parturition or on the survival, growth, or postnatal development of offspring. The systemic exposure reached in this study corresponds to approximately 6 times therapeutic clinical exposure in humans (based on the maximum serum concentration, C_{max}) at the proposed clinical dose of 6 mg.

Brolucizumab was not detected in the maternal milk or infant serum- of cynomolgus monkeys in the study.

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 embryo-fetal development.

OTHER INFORMATION

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

Shelf life
24 months.

Do not use after the EXPIRY DATE printed on the vial

Special precautions for storage

Keep out of the reach and sight of children.

Vial: Store in the original package. Protect from light. Store at 2 - 8°C. Do not freeze.

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

Pack Sizes

One 0.23 ml vial, one filter needle.

Patient Counseling Information

Advise patients that in the days following Pagenax administration, patients are at risk of developing endophthalmitis, retinal detachment, retinal vasculitis and/or retinal vascular occlusion. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision, instruct the patient to seek immediate care from an ophthalmologist [see Warnings and Precautions].

Patients may experience temporary visual disturbances after an intravitreal injection with Pagenax and the associated eye examination [see Adverse Effects]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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