NOVARTIS

VSIQQ®

(brolucizumab)

120 mg/mL solution for injection

Professional Information

Document status: Final

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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

VSIQQ® 120 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL solution for injection contains 120 mg of brolucizumab.

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

Each vial contains 27,6 mg brolucizumab in 0,23 mL solution. This provides a usable amount to deliver a single dose of 0,05 mL containing 6 mg of brolucizumab.

For the full list of excipients, see section 6.1.

Contains sugar: sucrose – A vial contains 13,3 mg sucrose

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

VSIQQ is indicated for the treatment of:

- Neovascular (wet) age-related macular degeneration (AMD).
- Diabetic macular edema (DME).

4.2 Posology and method of administration

Posology

VSIQQ must be administered by a qualified medical practitioner.

Age-related Macular Degeneration (Wet AMD)

Treatment initiation – loading

The recommended dose is 6 mg (0,05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first three doses. Alternatively, VSIQQ 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, VSIQQ is administered every 12 weeks (3 months). The medical practitioner may then individualise 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) (see section 5.1). 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 section 4.4).

Diabetic Macular Edema (DME)

The recommended dose for VSIQQ is 6 mg (0,05 mL) administered by intravitreal injection every 6 weeks for the first five doses. Thereafter, VSIQQ 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

Hepatic impairment

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

Renal impairment

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

Elderly (age 65 years and over)

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

Paediatric population

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

Method of administration

VSIQQ is for intravitreal use only.

VSIQQ should be inspected visually prior to administration (see section 6.6).

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

The injection needle should be inserted 3,5 to 4,0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0,05 mL is then delivered slowly; a different scleral site should be used for subsequent injections.

The safety and efficacy of VSIQQ administered in both eyes concurrently have not been studied and is not recommended.

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

Instructions for use of the VSIQQ vial kit

Storage and inspection

	Store VSIQQ in the refrigerator (2 °C to 8 °C); do not freeze. Keep the vial in the outer carton to protect from light.
	Prior to use, the unopened vial of VSIQQ may be kept at room temperature (below 25 °C) for up to 24 hours. After opening the vial, proceed under aseptic conditions.
	VSIQQ is a clear to slightly opalescent and colourless 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 VSIQQ

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 anaesthesia 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 30 G x ½” injection needle, sterile.

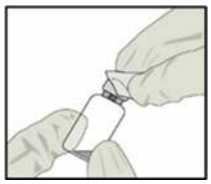
• A 1 mL syringe with a 0,05 mL dose mark, sterile

• The 5 µm blunt filter needle (18 G x 1½ ”, 1,2 mm x 40 mm), sterile

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

Note: The dose must be set to 0,05 mL.

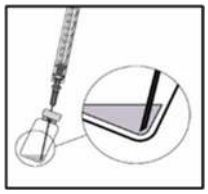
Ensure that the injection is given immediately after preparation of the dose (Step 8)

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 centre of the vial septum until the needle touches the bottom of the vial.

4 

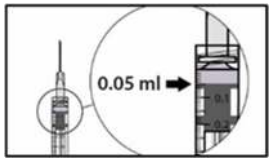
To withdraw the liquid, hold the vial **slightly inclined and slowly withdraw** all the liquid from the vial and filter needle. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

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

6 The filter needle is not to be used for intravitreal injection. Aseptically and **firmly assemble a 30 G 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 medicine or waste material should be disposed of in accordance with local regulations.

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.
- Pregnancy and lactation, see section 4.6

4.4 Special warnings and precautions for use

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

Intravitreal injections, including those with VSIQQ, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection techniques must always be used when administering VSIQQ. Retinal vasculitis and/or retinal vascular occlusion,

typically in the presence of intraocular inflammation, have been reported with the use of VSIQQ (see section 4.3 and section 4.8). These immune mediated adverse events may occur following the first intravitreal injection. Discontinue treatment with VSIQQ in patients who develop these events. Patients treated with VSIQQ who experience intraocular inflammation may be at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored.

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 VSIQQ every 4-week maintenance dosing experienced a higher incidence of intraocular inflammation (including retinal vasculitis) and retinal vascular occlusion than patients who received VSIQQ every 8- or 12-week maintenance dosing in the pivotal Phase III clinical studies (HAWK and HARRIER). The interval between two VSIQQ doses during maintenance treatment should not be less than 8 weeks (see section 4.2).

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). Sustained intraocular pressure increases have also been reported with VSIQQ. Both

intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately.

VSIQQ contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take VSIQQ.

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

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

Pregnancy

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 C_{max} (see Animal data). However, based on the anti-VEGF mechanism of action,

brolucizumab must be regarded as potentially teratogenic and embryo/foetotoxic. Therefore, brolucizumab should not be used during pregnancy. See section 4.3.

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 had blood and milk collected for toxicokinetic evaluations. There was no impact of IVT administration of brolucizumab on embryo-foetal development, pregnancy or parturition, or on the survival, growth, or postnatal development of offspring. This represents an exposure approximately 6-times the human exposure (based on serum C_{max}) at the proposed clinical dose of 6 mg.

Breastfeeding

Because of the potential for adverse drug reactions in the breastfed new-born/infant, breastfeeding is not recommended during treatment and for at least one month after the last dose when stopping treatment with VSIQQ. See section 4.3. In an ePPND study, brolucizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys.

Fertility

VEGF inhibition has been shown to affect follicular development, corpus luteum function and fertility. Based on the mechanism of action of VSIQQ, there is a potential risk for female reproduction, and to embryofoetal development.

4.7 Effects on ability to drive and use machines

Patients may experience temporary visual disturbances after an intravitreal injection with VSIQQ 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

a. Summary of the safety profile

Wet AMD population

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

The most frequently reported adverse drug reactions (in > 5 % of patients treated with VSIQQ) 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 < 1 % of the patients treated with VSIQQ were endophthalmitis, blindness, retinal artery occlusion and retinal detachment.

DME population

The safety of VSIQQ 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 VSIQQ and two patients (0,5 %) treated with aflibercept 2 mg. Retinal vasculitis was reported in one patient (0,3 %) treated with VSIQQ 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.

b. Tabulated summary of adverse reactions

Adverse reactions from the HAWK and HARRIER clinical studies (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency

grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1 Frequencies of adverse drug reactions in clinical studies

System organ class	**Frequency category**
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

Endophthalmitis	Uncommon
Blindness	Uncommon
Retinal artery occlusion	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
Immune system disorders	
Hypersensitivity [a)]	Common
[a)] Including urticaria, rash, pruritus, erythema	

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 VSIQQ via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

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

Eye disorders
Retinal vascular occlusion, retinal vasculitis
Scleritis

c. Description of selected adverse 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 VSIQQ 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 VSIQQ suggest that patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with VSIQQ were more likely to present with similar events after VSIQQ injection, as compared to nAMD patients with no history of these events.

Immunogenicity

There is a potential for an immune response in patients treated with VSIQQ. The immunogenicity of VSIQQ was evaluated in serum samples. The immunogenicity data reflect

the percentage of patients whose test results were considered positive for antibodies to VSIQQ in immunoassays.

Wet AMD

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

DME

The pre-treatment incidence of anti-brolucizumab antibodies was 64 %. After dosing with VSIQQ 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 VSIQQ. This treatment emergent antibody response may develop following the first intravitreal injection (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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

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

Mechanism of action

Increased levels of signalling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathologic 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.

Wet AMD

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

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

In the TALON study, related anatomical parameters were part of the disease activity assessments guiding treatment decisions. Reductions in central subfield thickness (CST) and reductions in presence of intraretinal/subretinal fluid (IRF/SRF) or sub-retinal pigment epithelium were observed in patients treated with VSIQQ at Weeks 32 and 64 (see section 5.1 Clinical efficacy and safety).

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 as early as 4 weeks after treatment initiation and up to Week 52. These reductions were maintained up to Week 100.

Clinical efficacy and safety

Treatment of wet AMD

In silico study

The results of the VSIQQ arms of the HAWK and HARRIER studies, where VSIQQ 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 VSIQQ 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 VSIQQ 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) The first co-primary endpoint of the study was the distribution of the last interval with no disease activity up to Week 32 with the primary objective to demonstrate that VSIQQ is superior to aflibercept 2 mg with respect to duration of treatment intervals at Week 32.

2) The second co-primary endpoint of the study was to demonstrate that VSIQQ 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) VSIQQ 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 VSIQQ vs. 19.8%, 39.9%, and 40.2% for aflibercept 2 mg, respectively (p-value <0.0001).

2) VSIQQ 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 VSIQQ 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 VSIQQ vs. 12.2%, 23.9%, 22.0%, 41.8% for aflibercept 2 mg, respectively. The average change in BCVA from baseline at Week 64 were +4.7 ETDRS letters vs. +4.9 ETDRS letters for VSIQQ and aflibercept 2 mg, 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 4.4) 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 VSIQQ vs. aflibercept 2 mg (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 VSIQQ vs. aflibercept 2 mg (50.3% vs. 56.6% and 54.2% vs. 65.9%). 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%).

TALON Extension Study

255 subjects who completed the TALON study were enrolled into a 56-week open label, one-arm extension study of TALON and treated with brolucizumab ‘treat-and-extend’ dosing regimen with a maximum treatment interval up to 20 weeks. At Week 56, more than 50% of 237 subjects who had received at least 2 injections were on a treatment interval of 16 weeks (24.9%) or 20 weeks (28.7%) and had no disease activity, while visual acuity was maintained throughout the study.

Treatment of DME

The safety and efficacy of VSIQQ were assessed in two randomized, multi-centre, 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 VSIQQ versus aflibercept 2 mg. In both studies, VSIQQ (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 VSIQQ 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 VSIQQ versus 15 in patients treated with aflibercept 2 mg.

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

Table 5 Efficacy outcomes at Weeks 52 and 100 in Phase III - KESTREL and KITE studies

		KESTREL			**KITE**		
Efficacy outcome	**At Week**	**VSIQQ (n=189)**	**aflibercept 2 mg (n=187)**	**Difference (95 % CI) VSIQQ – aflibercept**	**VSIQQ (n=179)**	**aflibercept 2 mg (n=181)**	**Difference (95 % CI) VSIQQ – aflibercept**
	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]

Change from baseline in BCVA (measured by ETDRS letters score) – LS mean (SE)	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 (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]
	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

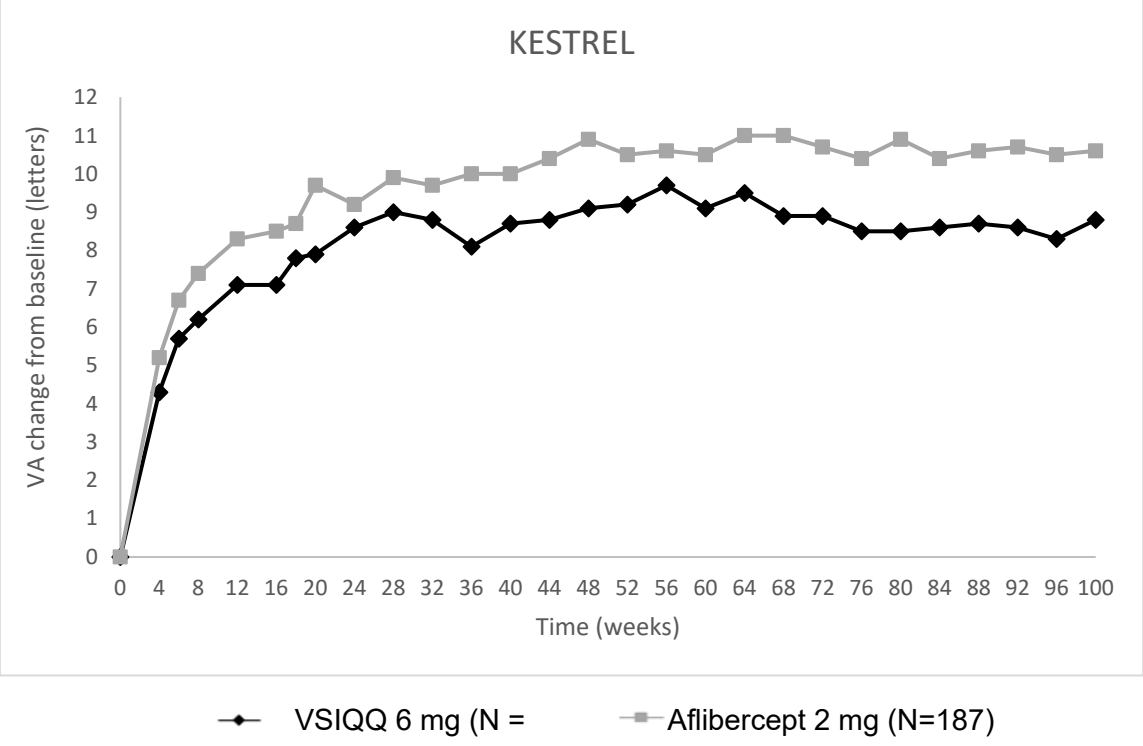
IRF: Intraretinal fluid; SRF: Subretinal fluid

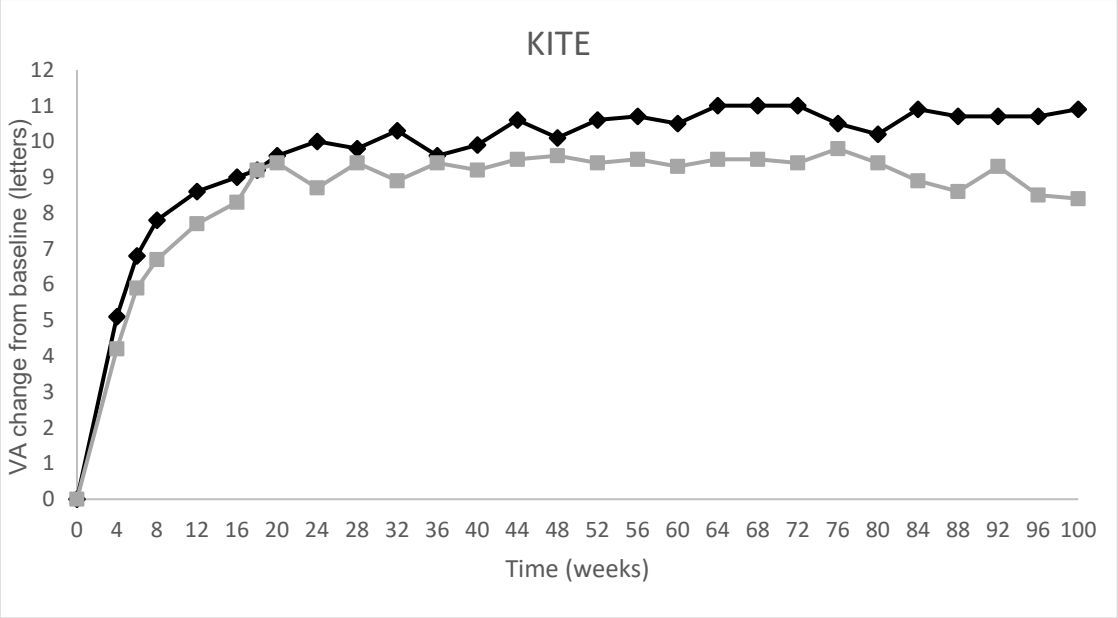
CST and fluid status assessments after start of alternative DME treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment

[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 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 VSIQQ on a q12w dosing interval at Week 52 and 44% and 37% of patients treated with VSIQQ 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 VISQQ 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 VSIQQ (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, VSIQQ 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 VSIQQ 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 VSIQQ (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 VSIQQ (42% KESTREL and 41% KITE) compared to patients treated with aflibercept 2 mg (54% KESTREL and 57% KITE).

In both studies, VSIQQ 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 VSIQQ 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 VSIQQ 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 VSIQQ and aflibercept 2 mg was 4.0 % (95 % CI: [-0.6, 8.6]). At Week 100, the proportion of patients with a ≥ 2 step improvement from baseline to Week 100 in the DRSS score was 32.8% with

VSIQQ and 29.3% with aflibercept 2mg in KESTREL and 35.8% with VSIQQ and 31.1% with aflibercept 2mg in KITE.

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption/ Distribution

After intravitreal administration of 6 mg brolucizumab per eye to patients with nAMD, the mean C_{max} of free brolucizumab in the plasma was 49,0 ng/mL (range: 8,97 to 548 ng/mL) and was attained in 1 day.

Elimination

Brolucizumab is a monoclonal antibody fragment and no medicine 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. VSIQQ did not accumulate in the serum when administered intravitreally every 4 weeks.

Special populations

Elderly (age 65 years and over)

In the HAWK and HARRIER clinical studies, approximately 90 % (978/1088) of patients randomised to treatment with VSIQQ were ≥ 65 years of age and approximately 60 % (648/1088) were ≥ 75 years of age. In the KESTREL and KITE clinical studies, approximately 45 % (164/368) of patients randomized to treatment with VSIQQ 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.

Renal impairment

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

The systemic clearance of brolucizumab was evaluated in nAMD patients who had both serum brolucizumab pharmacokinetic and creatinine clearance data available. Subjects with

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

Hepatic impairment

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/Nonclinical Toxicology

Carcinogenicity and mutagenicity

No studies have been conducted on the carcinogenic or mutagenic potential of VSIQQ.

Repeat dose toxicity

Preclinical 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate

Sucrose

Polysorbate 80

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator between 2 °C – 8 °C.

Do not freeze.

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

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

6.5 Nature and contents of container

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 (18 G x 1½ ″, 1,2 mm x 40 mm, 5 µm).

6.6 Special precautions for disposal

The solution should be inspected visually upon removal from the refrigerator and prior to administration. If particulates, cloudiness, or discolouration 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. Detailed instructions for use are provided in the package leaflet.

Any unused medicine or waste material should be disposed of in accordance with local regulations.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

54/15.4/0489

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 October 2020

10. DATE OF REVISION OF THE TEXT

15 May 2025