

**EVIDENCE BRIEFING
November 2018**

Ranibizumab for proliferative and non-proliferative diabetic retinopathy

NIHRIO ID	11177	NICE ID	8259
Developer/Company	Novartis Pharmaceuticals UK Ltd	UKPS ID	650369
Licensing and market availability plans	Currently in phase III clinical trials.		

SUMMARY

Ranibizumab as intravitreal injections is in clinical development for the treatment of diabetic retinopathy in both its proliferative and non-proliferative forms. Diabetic retinopathy, is a disease that affect the retinas and other parts of the inner eye. It is a chronic progressive condition of the retinal blood vessels due to prolonged raised blood glucose. When new blood vessels and scar tissue form on the retina causing bleeding within the eye and loss of vision, it is called proliferative diabetic retinopathy.

Ranibizumab has been designed to block a substance called vascular endothelial growth factor A (VEGF-A), a protein that helps blood vessels grow and leak fluid and blood. By blocking this factor, ranibizumab reduces the growth of the blood vessels and controls the leakage and swelling in the retina. If licensed for diabetic retinopathy, ranibizumab has the potential to neutralise the retinal macular degeneration and reverse disease progression.

PROPOSED INDICATION

Treatment of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) – first line^a

TECHNOLOGY

DESCRIPTION

Ranibizumab (Lucentis) is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and choroidal neovascularisation or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to retinal vein occlusion.¹

Ranibizumab is currently in development for the treatment of proliferative and non-proliferative diabetic retinopathy. In the phase III clinical trials²⁻⁴ (NCT01489189 or Protocol S; NCT00687804 or RESTORE and NCT00989989 or REVEAL) 0.5mg ranibizumab was administered as intravitreal injections at least once every 4 weeks.^a

INNOVATION AND/OR ADVANTAGES

The traditional treatments for PDR and the severe form of NPDR⁵ panretinal photocoagulation (PRP) and vitrectomy may lead to untoward effects, including visual field constriction, impaired night vision, decreased contrast sensitivity, retinal breaks, cataract progression, and deterioration of central vision resulting from exacerbation of macular edema.⁶

Addressing the underlying pathophysiologic feature common among NPDR and PDR: progressive retinal vascular deterioration by means of neutralization of pathologic levels of VEGF with anti-VEGF pharmacotherapies can reverse disease worsening and can promote retinopathy improvements, a process likely related to the stabilization and possible improvement of retinal circulation.⁶

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In its intravitreal injection formulation, ranibizumab is licensed in the UK for:⁷

- Neovascular (wet) age-related macular degeneration (specialist use only)
- Diabetic macular oedema (specialist use only)
- Macular oedema secondary to retinal vein occlusion (specialist use only)
- Choroidal neovascularisation (specialist use only)
- Concomitant treatment of diabetic macular oedema, or macular oedema secondary to branch retinal vein occlusion, with laser photocoagulation (specialist use only)

Adverse effects of ranibizumab include vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation, increased lacrimation, blepharitis, dry eye, ocular hyperaemia, eye pruritus, retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment

^a Information provided by Novartis on UK PharmaScan

epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia.¹

Ranibizumab is currently at phase III of development for retinopathy of prematurity.⁸

PATIENT GROUP

DISEASE BACKGROUND

Diabetic retinopathy (DR) is a progressive microangiopathy associated with both type 1 and type 2 diabetes mellitus that is mediated by hypoxia-induced upregulation of proangiogenic, proinflammatory, and vascular permeability factors, including VEGF-A.⁶

DR is defined as a chronic progressive, potentially sight-threatening disease of the retinal microvasculature associated with prolonged hyperglycaemia.⁹ It is classified according to the presence or absence of abnormal new vessels as: non-proliferative (background/pre-proliferative) retinopathy and proliferative retinopathy. Each has a different prognosis for vision. Non-proliferative diabetic retinopathy (NPDR) occurs when there are only intraretinal microvascular changes, such as altered retinal vascular permeability and eventual retinal vessel closure. Clinically, the hallmark of the non-proliferative phase is microaneurysms and intraretinal abnormalities.¹⁰ Proliferative diabetic retinopathy (PDR) is when new blood vessels and scar tissue have formed on the retina, which can cause significant bleeding and lead to retinal detachment.¹¹

Progression of NPDR to PDR has implications for clinical management, because PDR is associated with an increased occurrence of diabetic macular oedema (DMO) and fibroproliferative events, such as retinal traction, retinal detachment, and vitreous haemorrhage.⁶ The changes in NPDR typically do not produce noticeable symptoms in the early stages of the disease.¹²

Risk factors identified for the progression of retinopathy include:¹⁰

- Hypertension
- Elevated levels of serum cholesterol
- Pregnancy
- Other systemic risk factors such as albuminuria, proteinuria, or renal failure and anaemia. History of diabetic neuropathy and cardiovascular autonomic neuropathy have also been suggested to be associated with increased risk of progression of retinopathy.

Symptoms may occur as a result of a haemorrhage or detached retina which may include:¹³

- Sudden appearance of floaters (dots, specks or streaks) in your vision
- Effect similar to cobwebs across your vision
- Distorted shape of objects
- Loss of vision

CLINICAL NEED AND BURDEN OF DISEASE

DR is the most common form of eye disease amongst individuals with diabetes mellitus.¹⁴

In the UK, a cohort study regarding incidence and prevalence trends of DR based on data collected from the Clinical Practice Research Datalink between 2004 and 2014 identified a total of 144,362 prevalent cases of DR and established a 48.4% of DR in the population with type 1 diabetes mellitus (T1DM) and 28.3% in the population with type 2 diabetes mellitus (T2DM). A total of 9,085 prevalent cases of severe or proliferative DR were identified during the study period, 7.0% in the population with type 1 diabetes and 1.4% in the population with type 2 diabetes.¹⁵

Between April 2012 and March 2013 DR accounted for about 7% (or 1,592 cases) of people who were registered blind in England and Wales according to a research briefing done by Royal National Institute of Blind People.¹⁶

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

DR usually only requires specific treatment when it reaches an advanced stage and there is a risk to people's sight.^{5,17}

According to recent guidelines published by the International Council of Ophthalmology in 2017, treatment of DR involves optimizing medical treatment, improving glycaemic control if HbA1c > 58 mmol/mol (>7.5%) as well as associated systemic hypertension or dyslipidaemia. Patients with DR should be followed closely for development of PDR. Early panretinal photocoagulation should be considered for patients at high risk of progression to PDR or poor compliance with follow-up.¹⁸

Patients who have developed PDR should be treated with panretinal photocoagulation (PRP) with laser. These patients usually need numerous follow-up visits and may require supplementary laser treatment. PRP reduces the risk of visual loss and blindness. Although laser treatment is effective, some patients may still develop vitreous haemorrhage which is caused by the diabetes and not by the laser; it may mean the patient needs more laser treatment. Laser treatment often reduces peripheral and night vision; treatment may moderately reduce central vision.¹⁸

Vitrectomy may be considered in advanced active PDR that persists despite extensive PRP.¹⁸

Furthermore, the Royal College of Ophthalmologists, adds to the recommendations above that patients with diabetes who smoke should be made aware that they are at higher risk of cardiovascular disease and should be encouraged to quit as part of healthy life style advice.⁹

CURRENT TREATMENT OPTIONS

In the UK, the NHS offers the following current treatment options for DR that is threatening vision:¹⁷

- laser treatment – to treat the growth of new blood vessels at the back of the eye (retina) in cases of proliferative diabetic retinopathy, and to stabilise some cases of maculopathy
- intravitreal eye injections – to treat severe maculopathy that is threatening vision
- eye surgery – to remove blood or scar tissue from the eye if laser treatment is not possible because retinopathy is too advanced

PLACE OF TECHNOLOGY

There is increasing evidence from clinical trials demonstrating anti-VEGF injections (ranibizumab) as a safe and effective treatment of PDR through at least 2 years and that other intravitreal anti-VEGF

agents (i.e. aflibercept and bevacizumab) are also highly effective against retinal neovascularization.¹⁸ Five-year data emerging from the Protocol S study outlined below seems to support these findings.

If licensed in the UK for this indication, ranibizumab would be the first anti-VEGF agent to be used for the treatment of proliferative and non-proliferative diabetes retinopathy offering an additional treatment option for patients with PDR and NPDR that has the potential to reverse disease progression.

CLINICAL TRIAL INFORMATION

Trial	RESTORE, NCT00687804; adults aged 18 years and older; ranibizumab vs sham to ranibizumab administered as an intravitreal injection monotherapy or in combination with laser photocoagulation treatment or sham to laser procedure; phase III	RESTORE, NCT00687804; adults aged 18 years and older; phase III extension
Sponsor	Novartis Pharmaceuticals UK Ltd	-
Status	Complete and published	-
Source of Information	Trial registry ³ and publications ^{19,20}	Publication ²¹
Location	EU (incl UK), Canada, Turkey and Australia	-
Design	Randomised, laser-controlled, parallel assignment	Open label
Participants	n=345; aged 18 years and older; visual acuity impairment, diabetic macular oedema in at least one eye, type 1 or type 2 diabetes mellitus, medication for the diabetes treatment must be stable for the last 3 months.	n=240
Schedule	Randomised to: <ul style="list-style-type: none"> • Arm 1: Ranibizumab 0.5 mg administered monthly by intravitreal injection in the study eye for 3 months and ham laser treatment on day 1 and subsequently at intervals of at least 3 months. • Arm 2: Ranibizumab 0.5 mg administered monthly by intravitreal injection in the study eye for 3 months and active laser treatment on day 1 and subsequently at intervals of at least 3 months. • Arm 3: Laser photocoagulation treatment was administered on day 1 and at intervals of at least 3 months, if deemed 	Randomised to: <ul style="list-style-type: none"> • Arm 1: at the investigator's discretion, patients received open-label ranibizumab 0.5 mg intravitreal injections once a month until stable vision was reached (a maximum of 24 injections) and could receive laser therapy. • Arm 2: at the investigator's discretion, patients received open-label ranibizumab 0.5 mg intravitreal injections once a month until stable vision was reached (a maximum of 24 injections) and could receive laser therapy. • Arm 3: at the investigator's discretion, patients received

	necessary by the physician. Patients also received monthly sham intravitreal injection in the study eye for 3 consecutive months. Active/sham laser treatment was always administered before (sham) intravitreal injections. The minimum interval between the 2 treatments was 30 minutes.	open-label ranibizumab 0.5 mg intravitreal injections once a month until stable vision was reached (a maximum of 24 injections) and could receive laser therapy.
Follow-up	Active treatment for 3 months and then every three months if deemed necessary for the first 12 months	Follow up for 24 months. Overall follow-up 36 months.
Primary Outcomes	<ul style="list-style-type: none"> • Difference between the baseline level of visual acuity (Letters) of the study eye and the mean visual acuity averaged over all monthly post-baseline assessments from month 1 to month 12 [Time frame: baseline through the end of study (month 12)] 	<ul style="list-style-type: none"> • Percentage of participants with ocular adverse events (AEs) in the study eye in the 24 month extension study [Time frame: Extension baseline from month 12 (end of core study) to month 36 (end of extension study)] • Percentage of participants with non-ocular adverse events (AEs) in the 24 month extension study [Time frame: Extension baseline from month 12 (end of core study) to month 36 (end of extension study)]
Secondary Outcomes	<ul style="list-style-type: none"> • Categorized change in visual acuity (Letters) of the study eye from baseline at month 12 [Time frame: Baseline to month 12] • Mean change from baseline in visual acuity (Letters) of the study eye over time [Time frame: Baseline to month 12] • Mean change from baseline at month 12 in central retinal thickness of the study eye [Time frame: Baseline to month 12] • Mean change from baseline in patient-reported visual functioning [Time frame: Baseline to month 12] • Percentage of participants with ocular adverse events (AEs) in the study eye in the 36 months of the core and extension studies 	<ul style="list-style-type: none"> • Mean change from extension study baseline in best corrected visual acuity (BCVA) at month 36 [Time frame: Extension baseline month12 (end of core study)- month 36 (end of extension study)]

	<p>[Time frame: Core baseline (day 1 of the core study) to month 36 (end of extension study) [36 months]]</p> <ul style="list-style-type: none"> • Percentage of participants with non-ocular adverse events (AEs) in the 36 months of the core and Extension Studies [Time Frame: Core baseline (Day 1 of the core study) to month 36 (end of extension study) [36 months]] • Mean change from core study baseline in best corrected visual acuity (BCVA) at month 36 [Time frame: Core baseline (day 1 of the core study), month 36 (end of extension study)] 	
Key Results	<p>Mean baseline NEI VFQ-25 composite scores were 72.8, 73.5, and 74.1 in the ranibizumab, laser, and ranibizumab plus laser groups, respectively. At 12 months, the mean composite scores (95% CIs) improved by 5.0 (ranibizumab vs laser, 2.6 to 7.4; $P = 0.01$ vs laser) and 5.4 (ranibizumab plus laser vs laser alone, 3.3 to 7.4; $P = 0.004$ vs laser) from baseline in the ranibizumab and ranibizumab plus laser groups, respectively, compared with 0.6 (-1.8 to 3.0) for the laser group. Near activities scores improved by 9.0 (ranibizumab vs laser, 5.0 to 13.0; $P = 0.01$) and 9.1 (ranibizumab plus laser vs laser, 5.6 to 12.6; $P = 0.006$) compared with 1.1 (-3.0 to 5.2) for the laser group, whereas distance activities scores improved by 5.3 (ranibizumab vs laser, 1.8 to 8.9; $P = 0.04$) and 5.6 (ranibizumab plus laser vs laser, 2.3 to 9.0; $P = 0.03$) compared with 0.4 (-3.1 to 3.8) for the laser group. Patients with better baseline visual acuity or lower central retinal thickness had greater improvements with ranibizumab treatment compared with laser in composite and some subscale scores compared with patients with worse visual acuity or higher central retinal thickness.</p>	<p>Overall, 208 patients (86.7%) completed the extension study. In patients treated with ranibizumab during the core study, consecutive individualized ranibizumab treatment during the extension study led to an overall maintenance of BCVA and central retinal subfield thickness (CRST) observed at month 12 over the 2-year extension study (+8.0 letters, -142.1 μm [prior ranibizumab] and +6.7 letters, -145.9 μm [prior ranibizumab + laser] from baseline at month 36) with a median of 6.0 injections (mean, 6.8 injections; prior ranibizumab) and 4.0 (mean, 6.0 injections; prior ranibizumab + laser). In the prior laser group, a progressive BCVA improvement (+6.0 letters) and CRST reduction (-142.7 μm) at month 36 were observed after allowing ranibizumab during the extension study, with a median of 4.0 injections (mean, 6.5 injections) from months 12 to 35. Patients in all 3 treatment groups received a mean of <3 injections in the final year.</p>

	A subgroup analysis of the primary end point was performed on the basis of demographic and baseline disease characteristics. The key categories assessed were as follows: DME type (focal/diffuse), BCVA letter score (≤ 60 , 61–73, and >73), diabetes type (type 1/type 2), focal and/or grid laser pretreatment (yes/no), CRT (<300 , 300–400, and >400 μm), ETDRS retinopathy severity score (10–35, 43 or 47, and 53–85), macular ischemia (yes/no). Each of the ranibizumab patient subgroups did better on average than those on laser alone in terms of the primary efficacy end point.	
Adverse effects (AEs)	<p>Adverse events (AEs) and serious adverse events (SAEs) reported by groups as follows:</p> <ul style="list-style-type: none"> • Ranibizumab 0.5 mg group (83 participants): AEs 66.3; SAEs 2.4 • Ranibizumab 0.5 mg + Laser (83 participants): AEs 67.5; SAEs 3.6 • Laser With Ranibizumab in Extension (59 participants): AEs 64.4; SAEs 5.1 • Laser Without Ranibizumab in Extension (15 participants): AEs 46.7; SAEs 0 	No cases of endophthalmitis, retinal tear, or retinal detachment were reported. The most frequently reported ocular and non-ocular adverse effects over 3 years were cataract (16.3%) and nasopharyngitis (23.3%). Eight deaths were reported during the extension study, but none were suspected to be related to the study drug/procedure.
Expected reporting date	-	-

Trial	Protocol S, NCT01489189; adults aged 18 years and older; ranibizumab with deferred panretinal photocoagulation vs prompt panretinal photocoagulation alone; phase III
Sponsor	Jaeb Center for Health Research, National Eye Institute (NEI) and Genentech, Inc.
Status	Complete and published
Source of Information	Trial registry ² and publication ²²
Location	USA
Design	Randomised, laser-controlled
Participants	n=305; aged 18 years and older; Type 1 or type 2 diabetes mellitus; presence of PDR which the investigator intends to manage with PRP alone but for which PRP can be deferred for at least 4 weeks in the setting of intravitreal ranibizumab, in the investigator's judgment; best corrected Electronic-Early Treatment Diabetic

	Retinopathy Study (E-ETDRS) visual acuity letter score > 24 (approximate Snellen equivalent 20/320) on the day of randomization; media clarity, pupillary dilation, and study participant cooperation sufficient to administer PRP and obtain adequate fundus photographs and optical coherence tomography (OCT).
Schedule	<p>Randomised to:</p> <ul style="list-style-type: none"> • Arm 1: Intravitreal injection of 0.5 mg ranibizumab at baseline and up to every 4 weeks using defined retreatment criteria, in combination with deferred panretinal photocoagulation (PRP). • Arm 2: Panretinal photocoagulation alone at baseline (full session completed within 56 days).
Follow-up	Follow-up for 24 months.
Primary Outcomes	<ul style="list-style-type: none"> • Mean change in visual acuity from baseline [Time Frame: 2-years]
Secondary Outcomes	<ul style="list-style-type: none"> • Mean visual acuity [Time Frame: 2-years] • Number of eyes with greater than or equal to 10 letter vision gain [Time Frame: 2-years] • Humphrey visual field test cumulative score change from baseline [Time Frame: 2-years] • Frequency of vitrectomy [Time Frame: 2-years] • Mean change in OCT central subfield thickness from baseline [Time Frame: 2-years] • Development of central DME with vision impairment by 2-years [Time Frame: 2-years] • Number of eyes with vitreous haemorrhage [Time Frame: 2-years] • Number of eyes without active or regressed neovascularization on fundus photography at 2-years [Time Frame: 2-years] • Number of eyes with greater than or equal to 10 letter vision loss [Time Frame: 2-years]
Key Results	<p>Mean visual acuity letter improvement at 2 years was +2.8 in the ranibizumab group vs +0.2 in the PRP group (difference, +2.2; 95% CI, -0.5 to +5.0; P < 0.001 for non-inferiority). The mean treatment group difference in visual acuity area under the curve over 2 years was +4.2 (95% CI, +3.0 to +5.4; P < 0.001). Mean peripheral visual field sensitivity loss was worse (-23 dB vs -422 dB; difference, 372 dB; 95% CI, 213-531 dB; P < 0.001), vitrectomy was more frequent (15% vs 4%; difference, 9%; 95% CI, 4%-15%; P < 0.001), and DME development was more frequent (28% vs 9%; difference, 19%; 95% CI, 10%-28%; P < 0.001) in the PRP group vs the ranibizumab group, respectively. Eyes without active or regressed neovascularization at 2 years were not significantly different (35% in the ranibizumab group vs 30% in the PRP group; difference, 3%; 95% CI, -7% to 12%; P = 0.58).</p>

Adverse effects (AEs)	One eye in the ranibizumab group developed endophthalmitis. No significant differences between groups in rates of major cardiovascular events were identified.
Expected reporting date	-

ESTIMATED COST

Ranibizumab 10mg per 1 ml (Lucentis) 1.65mg/0.165ml solution for injection pre-filled syringes has an NHS indicative price of £551.00.⁷

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- No NICE guidance has been identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Ophthalmic Pathology Service (All Ages). D12/S(HSS)/b.

OTHER GUIDANCE

- NHS England. Service Specification no. 22. NHS Diabetic Eye Screening Programme. 2018-2019.²³
- ICO Guidelines for Diabetic Eye Care. International Council of Ophthalmology. 2017.¹⁸
- Diabetic Retinopathy Guidelines. The Royal College of Ophthalmologists. 2012.⁹

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