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HEALTH TECHNOLOGY BRIEFING
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Brolucizumab for visual impairment due to diabetic macular oedema

NIHRIO ID	24235	**NICE ID**	10185
Developer/Company	Novartis General Medicines	**UKPS ID**	652643

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Brolucizumab is in clinical development for the treatment of visual impairment due to diabetic macular oedema (DMO). DMO is a condition affecting the retina, the nerve layer at the back of the eye. The central part of the retina known as the macula, is responsible for fine detail vision, both for near (reading) and for distance. In patients with DMO, the fine meshwork of blood vessels supplying nutrients and oxygen to the macula become damaged and leaky due to the high levels of glucose in the bloodstream in some patients with diabetes. If left untreated, the leakage will potentially permanently damage the retinal nerve cells and eventually produce scarring, which can be irreversible.

Brolucizumab is administered by intravitreal injection. It works by binding with high affinity and blocking multiple isoforms of a substance called vascular endothelial growth factor A (VEGF-A). By blocking VEGF-A, brolucizumab reduces the growth of

the blood vessels and controls the leakage and swelling. Brolucizumab may confer advantages over currently available therapies, potentially allowing for less frequent dosing resulting in a reduced treatment burden. If licensed, will provide a treatment option for patients with visual impairment due to DMO.

PROPOSED INDICATION

Treatment of visual impairment due to diabetic macular oedema (DMO).[1,2]

TECHNOLOGY

DESCRIPTION

Brolucizumab (RTH258) Brolucizumab is a humanised monoclonal single chain Fv (scFv) antibody fragment with a molecular weight of ~26 kDa. Increased levels of signalling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathological ocular angiogenesis and retinal oedema. Brolucizumab binds with high affinity to VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$, and $VEGF_{165}$), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A binding, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability.[3]

Brolucizumab is in clinical development for the treatment of patients with visual impairment due to diabetic macular oedema (DMO). In the phase III clinical trials (KESTREL; NCT03481634) and (KITE; NCT03481660), patients received intravitreal injections of brolucizumab 3mg/0.05ml, 5 loading doses (KESTREL) and brolucizumab 6 mg/0.05 ml, 5 loading doses (KITE) with subsequent doses per protocol-specified maintenance schedule for both doses.[1,2]

INNOVATION AND/OR ADVANTAGES

Brolucizumab is a humanised monoclonal scFv and clinically the most advanced scFv fragment to reach this stage of development.[4] The proprietary innovative structure results in a small molecule (26 kDa) allowing it to achieve high doses in a single intravitreal injection, potent inhibition of all isoforms of VEGF-A, better retinal and choroidal penetration and faster systemic clearance.[5,6] Combined with excellent biophysical properties such as high solubility and stability, up to 6 mg can be administered, which represents a molar excess higher than 10- and 20-fold over aflibercept and ranibizumab clinical doses, respectively. Therefore, brolucizumab may confer advantages over currently available therapies, potentially allowing for less frequent dosing resulting in a reduced treatment burden.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Brolucizumab is currently licensed in the UK for the treatment of neovascular (wet) age-related macular degeneration (wAMD).[3]

The most common side effects with brolucizumab (which may affect up to 1 in 10 people) are reduced visual acuity, cataract (clouding of the lens in the eye), conjunctival haemorrhage (bleeding at the front of the eye) and vitreous floaters (spots in the vision).[8]

Brolucizumab is in phase III clinical development for DMO and retinal vein occlusion with ongoing phase IIIb studies in neovascular (wet) Age-related Macular Degeneration and Diabetic Macular Oedema.[9]

PATIENT GROUP

DISEASE BACKGROUND

Diabetic macular oedema (DMO) is a common complication associated with diabetic retinopathy and is the most common cause of visual impairment in diabetes mellitus. It occurs as a result of changes in retinal blood vessels in people with diabetes. Disruption of the blood-retinal barrier allows fluid to leak from blood vessels in the central part of the retina (the macula), leading to fluid accumulation and thickening of the macula.[10] This can lead to severe visual impairment in the affected eye. DMO is a chronic condition and affects the central vision. Central vision can also be affected by the growth of abnormal vessels that cause bleeding within the eye which can lead to complete blindness.[11]

Risk factor for DMO include poor glucose control over a long period, increased the length of living with diabetes, types of diabetes, very high blood pressure, fluid retention, kidney disease, high-fat levels in the blood and pregnancy.[12] The most common symptoms of DMO include distortion and blurring of central vision and this usually results in difficulty with detailed visual tasks such as reading, watching television, driving and recognising faces.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Currently, the number of people diagnosed with diabetes in the UK is estimated at 3.5 million. It is predicted that up to 549,000 people in the UK have diabetes that is yet to be diagnosed. This means that, including the number of undiagnosed people, there is estimated to be over 4 million people living with diabetes in the UK at present.[14]

There are 1,686 people in England presenting each year with visual impairment because of DMO with a central retinal thickness of 400 micrometres or more. A further 4,519 people from the prevalent population have the disease that will progress from having a retinal thickness > 400 micrometres to more than 400 micrometres each year.[15]

Hospital Episodes Statistics data for England in 2018-19 recorded 2,401 finished consultant episodes (FCEs) for insulin-dependent diabetes mellitus with ophthalmic complications (ICD-10 code: E10.3) and non-insulin-dependent diabetes mellitus with ophthalmic complications (ICD-10 code: E11.3) leading to 2,030 admissions, 1,446 day cases and 3,065 bed days.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Good management of diabetes and other risk factors may delay the onset and progression of DMO and may involve diet and lifestyle modification, blood pressure control and pharmacological treatments.[10] Treatment for macular oedema is determined by the type of oedema. The most effective treatment pathway first aims to address the underlying cause of macular oedema, such as diabetes or high blood pressure, and then directly treat the damage in the retina.[17] For DMO specifically, the main treatment options in the UK include laser photocoagulation and pharmacological options.[10]

CURRENT TREATMENT OPTIONS

Currently NICE recommends the following options for the treatment of visual impairment due to diabetic macular oedema: [18,19]

Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema only if

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
- the company provides aflibercept with the discount agreed in the patient access scheme

Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal

Dexamethasone intravitreal implant is recommended as an option for treating diabetic macular oedema only if:

- the implant is to be used in an eye with an intraocular (pseudophakic) lens and
- the diabetic macular oedema does not respond to non-corticosteroid treatment, or such treatment is unsuitable

PLACE OF TECHNOLOGY

If licensed, brolucizumab will provide an additional treatment option for visual impairment due to diabetic macular oedema.

CLINICAL TRIAL INFORMATION

Trial	**KESTREL**, **NCT03481634**, EudraCT 2017-004742-23; A two-year, three-arm, randomized, double-masked, multicenter, phase III study assessing the efficacy and safety of

	brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema **Trial phase** III- Active, not recruiting **Location(s):** EU (including UK), Canada, USA and other countries **Primary completion date:** November 2020
Trial design	Randomised, parallel assignment, double-blinded
Population	N= 571; aged 18 years and older; type 1 or type 2 diabetes mellitus; HbA1c of ≤ 10 at screening
Intervention(s)	Brolucizumab 3 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule
Comparator(s)	Aflibercept 2 mg/0.05 mL, as labelled, 5 loading doses, with subsequent doses every 8 weeks
Outcome(s)	Change from baseline in best-corrected visual acuity (BVCA) at week 52 (Time frame: baseline, week 52) See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**KITE, NCT03481660, EudraCT- 2017-003960-11;** A two-year, two-arm, randomized, double masked, multicenter, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema **Phase III**- Active, not recruiting **Location(s):** EU (not UK) and other countries **Primary completion date:** June 2020
Trial design	Randomised, parallel assignment, double-blinded
Population	N= 363; 18 years and older; type 1 or type 2 diabetes mellitus; HbA1c of ≤10% at screening
Intervention(s)	Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule
Comparator(s)	Aflibercept 2 mg/0.05 mL, as labelled, 5 loading doses, with subsequent doses every 8 weeks

Outcome(s)	Change from baseline in BCVA at week 52 (time frame: baseline, week 52) See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Brolucizumab is already marketed in the UK for wAMD. The NHS indicative price is:[20]

- 19.8mg/0.165ml solution for injection pre-filled syringes costs £ 816.00 (Hospital only)

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Aflibercept for treating diabetic macular oedema (TA346). July 2015.
- NICE technology appraisal guidance. Dexamethasone intravitreal implant for treating diabetic macular oedema (TA349). July 2015.
- NICE technology appraisal guidance. Ranibizumab for treating diabetic macular oedema (TA274). May 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- American Society of Retina Specialists. Evidence-Based Guidelines for Management of Diabetic Macular Edema. 2019.[21]
- American Academy of Ophthalmology. Guidelines on Diabetic Eye Care. The International Council of Ophthalmology Recommendations for Screening, Follow-up, Referral, and Treatment Based on Resource Settings. 2018.[22]
- Ophthalmologica. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). 2017.[23]
- International Council of Ophthalmology. ICO Guidelines for Diabetic Eye Care. 2017.[24]
- The Royal College of Opthalmologists. Diabetic Retinopathy Guidelines. 2012.[25]
- Centre for Eye Research. Diabetic Retinopathy Management Guidelines. 2012.[26]

ADDITIONAL INFORMATION

REFERENCES

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