Health Technology Briefing
May 2022

Ranibizumab port delivery system for treating diabetic macular oedema

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28429	NICE ID: 10549	UKPS ID: 658593

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

The port delivery system with ranibizumab (PDS) is in clinical development for the treatment of diabetic macular oedema (DMO). DMO is swelling of the macula caused by diabetes or by blockage of the veins behind the retina and it is the most common cause of sight loss in people with diabetes. DMO occurs when blood vessels damaged by high blood sugar leak into the central area of the retina (macular) resulting in a fluid build-up. The risk of developing DMO is greater for people who have had diabetes for a long time, have poorly controlled blood sugar, have high blood pressure, have high cholesterol levels, smoke and are pregnant.

Ranibizumab is a small piece of a monoclonal antibody, which is a type of protein that recognises and attaches to a specific target (called an antigen) that is found in certain cells in the body. Ranibizumab attaches to and blocks a substance called vascular endothelial growth factor A (VEGF-A). VEGF-A is a protein that makes blood vessels grow and leak fluid and blood, damaging the macula. By blocking VEGF-A, ranibizumab reduces the growth of the blood vessels and controls the leakage and swelling. The ranibizumab PDS is a long-acting drug delivery system which enables the continuous delivery of ranibizumab into the vitreous (the jelly-like fluid in the eye). It includes a permanent, refillable implant that is surgically inserted. If licensed, ranibizumab PDS would benefit DMO patients by providing up to six months of uninterrupted therapy that could potentially improve vision outcomes.

Proposed Indication

The treatment of diabetic macular oedema (DMO).[1]

Technology

Description

Ranibizumab (Lucentis) belongs to a class of drugs that blocks the action of vascular endothelial growth factor A (VEGF-A). In DMO, VEGF-A causes blood vessels to leak in the macula, the area of the retina responsible for the clearest vision. The accumulated fluid causes swelling, or oedema, which impairs vision. By inhibiting the action of VEGF-A, ranibizumab reduces oedema and limits visual loss or improves vision.[2] The port delivery system (PDS) with ranibizumab is a long-acting drug delivery system which enables the continuous delivery of ranibizumab into the vitreous. The PDS includes a permanent, refillable implant that is surgically inserted. A self-sealing septum allows drug replenishment without the need to remove the implant from the eye. Ranibizumab moves by passive diffusion down a concentration gradient from the implant reservoir and into the vitreous cavity. This passive diffusion results in the controlled continuous release of ranibizumab into the vitreous over time.[3]

The ranibizumab PDS is currently in clinical development for the treatment of DMO. In the phase III trial, (NCT04108156, Pagoda), the PDS implant pre-filled with 100 mg/mL ranibizumab will be surgically inserted and refill-exchange procedures will be performed on a fixed interval every 24 weeks (Q24W) thereafter.[1]

Key Innovation

Ranibizumab is currently administered via intravitreal injection and optimal results require frequent trips to a healthcare professional for eye injections. If licensed, the ranibizumab PDS would benefit DMO patients by providing up to six months of uninterrupted therapy that could potentially improve vision outcomes.[4]

Regulatory & Development Status

The ranibizumab PDS is not licensed for any indications in the EU/UK.

The ranibizumab PDS is currently in phase III/II clinical trials for the following indications:[5,6]

- Neovascular age-related macular degeneration
- Subfoveal neovascular age-related macular degeneration
- Wet age-related macular degeneration
- Diabetic retinopathy without DMO

Ranibizumab intravitreal injection is currently licensed in the UK for the following indications:[7,8]

- Neovascular (wet) age-related macular degeneration
- DMO
- Macular oedema secondary to retinal vein occlusion
- Choroidal neovascularization
- Concomitant treatment of DMO, or macular oedema secondary to branch retinal vein occlusion, with laser photocoagulation
- Proliferative diabetic retinopathy
- Retinopathy of prematurity with zone I, zone II or AP-ROP disease

Patient Group

Disease Area and Clinical Need

DMO is the most common cause of sight loss in people with diabetes. It affects the central area of the retina, called the macula, which is responsible for fine detail vision both near and far away. DMO occurs when blood vessels damaged by high blood sugar leak into the macular region resulting in a fluid build-up.[9,10] This build-up of fluid causes swelling of the macula which can impair sight. People with type 1 and type 2 diabetes are at risk of DMO. The risk of developing DMO is greater for people who have had diabetes for a long time, have poorly controlled blood sugar, have high blood pressure, have high cholesterol levels, smoke and are pregnant.[11] In the early stages of diabetes a person may not notice any effect on their vision. Damage to the retina occurs over many years. However, when the blood vessels in or close to the macula become damaged, or there is sudden bleeding or fluid leaking into the macula, then sight can worsen dramatically.[9]

According to the UK's national ophthalmology database study in 2013, clinically significant macular oedema was present in 6,664 eyes, 13.9% of the total number of diabetic eyes with structured assessment data at the time of their last record.[12] The prevalence of DMO in the UK diabetic population is approximately 7%.[13] In England (2020/21), there were 581 hospital admissions for patients with type 1 diabetes with ophthalmic complications (ICD-10 code E10.3, which includes DMO), and 839 finished consultant episodes (FCEs), resulting in 1,510 FCE bed days and 293 day cases. There were 962 hospital admissions for patients with type 2 diabetes with ophthalmic complications (ICD-10 code E11.3, which includes DMO), and 1,287 FCEs, resulting in 2,110 FCE bed days and 535 day cases.[14]

Recommended Treatment Options

DMO is usually treated with either laser treatment or intravitreal injections.[15] NICE recommends pharmacological therapies for DMO in eyes with central retinal thickness (CRT) >400 µm. These can either be anti-VEGF injections or steroids. NICE currently recommends the following therapies for the treatment of DMO:[16]

- Ranibizumab
- Aflibercept
- Fluocinolone acetonide
- Dexamethasone

Clinical Trial Information

Trial	**Pagoda, NCT04108156;** A Phase III, Multicentre, Randomized, Visual Assessor-Masked, Active-comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Diabetic Macular Oedema **Phase III –** Active, not recruiting **Location:** USA **Primary completion date:** Sep 2022
Trial Design	Randomised, parallel assignment, single-blinded, active-controlled
Population	N=545 (estimated); subjects with documented diagnosis of diabetes mellitus (type 1 or type 2); aged 18 years and older.
Intervention(s)	PDS implant pre-filled with 100mg/mL ranibizumab
Comparator(s)	Intravitreal ranibizumab 0.5mg injection

Outcome(s)	Primary outcome: Change in Best-Corrected Visual Acuity (BCVA) score from baseline averaged over weeks 60 and 64 as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart in the efficacy population [Time frame: baseline to week 64] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of the ranibizumab PDS is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Brolucizumab for treating diabetic macular oedema (GID-TA10794). Expected date of publication: November 2022.
- NICE technology appraisal in development. Faricimab for treating diabetic macular oedema (GID-TA10798). Expected date of publication: June 2022
- NICE technology appraisal. Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous therapy (TA613). November 2019.
- NICE technology appraisal. Dexamethasone intravitreal implant for treating diabetic macular oedema (TA349). July 2015.
- NICE technology appraisal. Aflibercept for treating diabetic macular oedema (TA346). July 2015.
- NICE technology appraisal. Ranibizumab for treating diabetic macular oedema (TA274). February 2013.
- NICE clinical guideline. Type 2 diabetes in adults: management (NG28). December 2015.
- NICE clinical guideline. Type 1 diabetes in adults: diagnosis and management (NG17). August 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology Services (Adult). A03/S/a

Other Guidance

- Amoaku et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. 2020.[16]
- Scottish Intercollegiate Guidelines Network. Management of diabetes: a national clinical guideline. 2017.[17]
- European Society of Retina Specialists (EURETINA). Guidelines for the management of diabetic macular oedema. 2017.[18]
- The Royal College of Ophthalmologists. Diabetic retinopathy guidelines. 2012.[19]

Additional Information

References

1 Clinicaltrials.gov. *This Study Will Evaluate the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System With Ranibizumab in Participants With Diabetic Macular Edema Compared With Intravitreal Ranibizumab (Pagoda). Trial ID: NCT04108156*. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT04108156 [Accessed 30 March 2022].

2 National Institute for Health and Care Excellence. *Ranibizumab for treating diabetic macular oedema* (*TA274)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta274 [Accessed 30 March 2022].

3 Campochiaro PA, Marcus DM, Awh CC, Regillo C, Adamis AP, Bantseev V, et al. The Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration: Results from the Randomized Phase 2 Ladder Clinical Trial. *Ophthalmology*. 2019;126(8):1141-54. Available from: https://doi.org/https://doi.org/10.1016/j.ophtha.2019.03.036.

4 Roche. *FDA accepts application for Roche's Port Delivery System with ranibizumab (PDS) for treatment of neovascular or "wet" age-related macular degeneration (nAMD).* 2021. Available from: https://www.roche.com/media/releases/med-cor-2021-06-24 [Accessed 30 March 2022].

5 Clinicaltrials.gov. *Search of: Port Delivery System With Ranibizumab.* 2022. Available from: https://clinicaltrials.gov/ct2/results?term=Port+Delivery+System+With+Ranibizumab&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&recrs=m&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 21 April 2022].

6 Roche. *Product Development Portfolio.* 2022. Available from: https://www.roche.com/solutions/pipeline/ [Accessed 3 May 2022].

7 National Institute for Health and Care Excellence. *Ranibizumab.* Available from: https://bnf.nice.org.uk/drug/ranibizumab.html [Accessed 6 April 2022].

8 Electronic Medicines Compendium. *Lucentis 10 mg/ml solution for injection.* 2022. Available from: https://www.medicines.org.uk/emc/product/307/smpc [Accessed 9 May 2022].

9 Macular Society. *Diabetic macular oedema.* Available from: https://www.macularsociety.org/macular-disease/macular-conditions/diabetic-macular-oedema/ [Accessed 30 March 2022].

10 National Health Service. *Treatments for Patients with Diabetic Macular Oedema (DMO).* 2019. Available from: https://www.hey.nhs.uk/patient-leaflet/treatments-patients-diabetic-macular-oedema-dmo/ [Accessed 30 March 2022].

11 Moorfields Eye Hospital. *Diabetic macular oedema.* Available from: https://www.moorfields.nhs.uk/condition/diabetic-macular-oedema [Accessed 1 April 2022].

12 Keenan TDL, Johnston RL, Donachie PHJ, Sparrow JM, Stratton IM, Scanlon P. United Kingdom National Ophthalmology Database Study: Diabetic Retinopathy; Report 1: prevalence of centre-involving diabetic macular oedema and other grades of maculopathy and retinopathy in hospital eye services. *Eye*. 2013;27(12):1397-404. Available from: https://doi.org/10.1038/eye.2013.196.

13 National Institute for Health and Care Excellence. *Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema (part review of TA301).* 2018. Available from: https://www.nice.org.uk/guidance/ta613/documents/final-scope#:~:text=Approximately%207%25%20of%20people%20with,nephropathy%2C%20obesity%20and%20high%20cholesterol. [Accessed 21 April 2022].

14 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 30 March 2022].

15 Manchester University NHS Foundation Trust. *Treatment of Diabetic Macular Oedema.* 2018. Available from: https://mft.nhs.uk/app/uploads/sites/2/2018/04/REH-217.pdf [Accessed 8 April 2022].

16 Amoaku WM, Ghanchi F, Bailey C, Banerjee S, Downey L, Gale R, et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. *Eye (Lond)*. 2020;34(Suppl 1):1-51. Available from: https://doi.org/10.1038/s41433-020-0961-6.

17 Scottish Intercollegiate Guidelines Network. *Management of diabetes: a national clinical guideline* (*116)*. Last Update Date: November 2017. Available from: https://www.sign.ac.uk/media/1054/sign116.pdf [Accessed 6 April 2022].

18 Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica*. 2017;237(4):185-222. Available from: https://doi.org/10.1159/000458539.

19 The Royal College of Ophthalmologists. *Diabetic Retinopathy Guidelines.* 2012. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2021/08/2012-SCI-267-Diabetic-Retinopathy-Guidelines-December-2012.pdf [Accessed 6 April 2022].

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