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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2020

Ranibizumab port delivery system for the treatment of age-related macular degeneration

NIHRIO ID	26950	**NICE ID**	10353
Developer/Company	Roche Products Ltd	**UKPS ID**	658594

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Ranibizumab port delivery system (PDS) is in clinical development for the treatment of neovascular age-related macular degeneration (nAMD). nAMD or wet age-related macular degeneration is a chronic eye disease characterised by the formation and proliferation of blood vessels in the centre of the retina (a layer of tissue in the back of the eye that senses light and sends images to the brain). nAMD is a leading cause of central sight loss and blindness. nAMD is linked to smoking, being overweight and high blood pressure amongst other risk factors. Symptoms include blurred vision, objects looking smaller, hallucinations and straight lines look crooked. Current treatment options include anti-VEGF-A therapies which are the current standard of care. This treatment would offer an alternative administration route for the already licensed ranibizumab. Frequent injections are a burden to patients; PDS would reduce this.

Ranibizumab is a type of antibody that is targeted against a particular protein. Ranibizumab has been designed to attach to and block 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 (the central part of the retina). By blocking VEGF-A, ranibizumab reduces the growth of the blood vessels and controls

the leakage and swelling. The port delivery system (PDS) will include a device which is permanently surgically implanted in the eye and filled with a special formulation of ranibizumab; this will reduce the amount of hospital visits required and reduce the burden of repeat intravitreal injections. If licensed, this technology will provide an additional treatment option for patients with nAMD.

PROPOSED INDICATION

Patients with neovascular age-related macular degeneration (nAMD).[a]

TECHNOLOGY

DESCRIPTION

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A).[1] 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 CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO in adults and retinopathy of prematurity in preterm infants.[1]

The port delivery system with ranibizumab (PDS) is a novel, innovative, long-acting drug delivery system with the potential to reduce treatment burden while maintaining optimal vision outcomes by enabling the continuous delivery of a customised formulation of ranibizumab into the vitreous. The PDS includes a permanent, refillable implant that is surgically inserted through a small incision in the sclera and pars plana. A self-sealing septum in the centre of the implant flange allows access to the implant reservoir for 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, through a porous metal release control element specifically designed for ranibizumab, and into the vitreous cavity. This passive diffusion through the release control element results in the controlled continuous release of ranibizumab into the vitreous over time.[2]

In phase III clinical trials (NCT03677934, NCT03683251), patients received 100 mg/mL ranibizumab delivered through the PDS in the study eye on day 1 and receive refills at fixed 24-week intervals.[3,4]

INNOVATION AND/OR ADVANTAGES

PDS contains a customised formulation of ranibizumab not approved by regulatory authorities.[5]

[a] Information provided by Roche Products Ltd on UK PharmaScan

By maintaining therapeutic drug concentration levels of ranibizumab with two refills per year, PDS may offer greater outcomes certainty in terms of vision gains and maintaining those gains for people living with nAMD.[5] The PDS is a long-term drug-delivery device, using a customized formulation of ranibizumab, which could reduce the burden of repeat intravitreal injections and the burden of frequent monitoring visits.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The ranibizumab PDS does not have Marketing Authorisation in the EU/UK for any indication.

Ranibizumab PDS is currently in phase III clinical trials for the treatment of diabetic retinopathy and diabetic macular oedema.[6]

In the phase II Ladder trial, more ocular adverse effects were observed in the PDS arms than in the monthly intravitreal ranibizumab injection arm. The most frequent serious adverse effect was vitreous haemorrhage, occurring in 7 patients (3.9%) in the overall PDS-treated population.[2]

PATIENT GROUP

DISEASE BACKGROUND

Age-related macular degeneration (AMD) is the most common cause of visual impairment in the developed world, and the Royal National Institute of Blind People (RNIB) reports that AMD is the most common cause of certification for vision impairment.[7] There are two main types of AMD, wet (neovascular) and dry (non- neovascular) AMD.[8]

Wet AMD (nAMD) is characterised by the formation of immature blood vessels that grow between the retinal pigment epithelial cells and the photoreceptor cells in the centre of the retina. This is known as choroidal neovascularisation (CNV). These blood vessels easily haemorrhage and cause scarring in the macula leading to vision impairment. A protein known as vascular endothelial growth factor (VEGF), which induces new blood vessel formation (angiogenesis), vascular permeability and inflammation, has been implicated in the development and progression of CNV. CNV can be subdivided into classic and occult forms according to its appearance on investigation by fluorescein angiography. A mixture of classic and occult CNV can occur in the same lesion. CNV can also be described in terms of its location: the fovea is the central part of the macula, and CNV that develops below the foveal area is termed 'subfoveal CNV'.[8]

The condition usually affects people who are over 50 years old and the risk increases significantly with age.[8] The most commonly cited risk factor for AMD is cigarette smoking; the risk of developing AMD is 3.6 times greater for current and former smokers than for people who have never smoked.[8] Hypertension, obesity, lack of exercise, a diet high in fat, a diet low in omega 3 and 6 and a family history of nAMD are also common risk factors.[7]

nAMD accounts for 10% of all cases of AMD, but about 60% of those are considered advanced at presentation. Progression of nAMD varies from a few months to three years. If left untreated, the diagnosis is poor with a significant visual loss (6/60 or worse) occurring within two to three years.[9]

People with macular degeneration retain their peripheral vision but lose central vision. Loss of central vision, particularly when affecting both eyes, is associated with a loss of quality of life,

affecting the ability to read, recognise faces and drive, and with an increased risk of falls and potentially significant loss of independence.[8]

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of late AMD in the UK among people aged 50 years or over is 2.4% (from a meta-analysis applied to UK 2007–09 population data). This increases to 4.8% in people aged 65 years or over, and 12.2% in people aged 80 years or over.[10] The prevalence of nAMD in the UK among people aged 50 years and over is between 1.2 and 6.3%.[7] Estimates indicate that around 39,800 people develop nAMD in the UK each year.[7]
There has been a significant increase in hospital activity in England for episodes with a primary diagnosis of AMD, from less than 10,000 episodes in the years 2005/06 to over 75,000 episodes in the years 2013/14.[7]

Due to the aging population, the number of people with nAMD will increase during the next decades.[11]

The company estimates that the eligible population will be between 500 and 750 per 100,000.[b]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Visual rehabilitation, with teaching of skills and the provision of equipment to facilitate reading and other activities of daily living, may help people make the most of their remaining vision in those with dry AMD. However, the aim of therapy for people with wet AMD is to alter the progression of vision loss.[12] In wet AMD, to stop vision loss from progressing regular eye injections and, very occasionally, photodynamic therapy is recommended.[13]

CURRENT TREATMENT OPTIONS

According to NICE guidelines for age-related macular degeneration the following pharmacological are considered for patients with wet AMD:[7]

- Ranibizumab
- Aflibercept

PLACE OF TECHNOLOGY

If licensed, ranibizumab PDS will offer an additional treatment option for patients with nAMD

CLINICAL TRIAL INFORMATION

Trial	**Archway; NCT03677934;** 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	**Portal; NCT03683251**; A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of the Port Delivery System With Ranibizumab in

[b] Information provided by Roche Products Ltd on UK PharmaScan

	Neovascular Age-Related Macular Degeneration **Phase III** - Active, not recruiting **Location:** US **Primary completion date:** March 2020	Patients With Neovascular Age-Related Macular Degeneration **Phase III** – Recruiting **Location:** US **Primary completion date**: September 2025
Trial design	Randomised, parallel assignment, single-blinded, active-controlled	Non-randomised, parallel assignment, single-blinded
Population	N=418; 50 years and older; previous treatment with at least three anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections for nAMD per standard of care within 6 months prior to the screening visit	N=1000; 50 years and older; previous enrolment in and completion of study GX28228 (Ladder) or study GR40548 (Archway), without early treatment or study discontinuation in either study
Intervention(s)	Ranibizumab; PDS implant with ranibizumab 100mg/ml refill-exchange given at fixed 24-week intervals	Ranibizumab; PDS implant with ranibizumab 100mg/ml refill-exchange given at fixed 24-week intervals
Comparator(s)	Ranibizumab; 0.5mg intravitreal injection given monthly	No comparator
Outcome(s)	Change from Baseline in Best-Corrected Visual Acuity (BCVA) Score at the Average of Week 36 and Week 40, as Assessed Using the ETDRS Visual Acuity Chart at a Starting Distance of 4 Meters [Time Frame: Baseline to Week 40] See trial record for full list of other outcomes	• Incidence and Severity of Ocular and Systemic (Non-Ocular) Adverse Events (AEs) [Time Frame: Baseline up to Week 144] • Incidence, Severity, and Duration of Adverse Event of Special Interest (AESIs) [Time Frame: Baseline up to Week 144] • Incidence, Severity, and Duration of PDS-Associated Ocular AESIs During the Postoperative Period (Up to 37 days of Initial Implantation) and Follow-Up Period (>37 days After Implantation Surgery) for Participants who Receive the PDS Implant in the Study [Time Frame: Baseline up to Week 144] See trial record for full list of other outcomes
Results (efficacy)	• Patients gained an average of 0.2 eye chart letters in visual acuity from baseline, with	-

	98.4% (n=244/248) of patients maintaining the fixed six-month refill schedule within the first refill period. Patients treated monthly with ranibizumab injections gained an average of 0.5 letters in visual acuity from baseline. According to pre-specified study criteria, PDS was shown to be non-inferior and equivalent to monthly ranibizumab injections. • In addition, PDS controlled retinal thickness as effectively as monthly ranibizumab, with patients in both arms achieving a mean change in center point thickness within 10 µm from baseline.[5]	
Results (safety)	Safety data from the study support a favourable benefit-risk profile for PDS. The PDS implant insertion surgery and refill-exchange procedures were generally well-tolerated by patients and the systemic safety of PDS was comparable to monthly ranibizumab injections.[5]	-

Trial	**LADDER; NCT02510794;** A Phase II, Multicenter, Randomised, Active Treatment-Controlled Study of the Efficacy and Safety of the Ranibizumab Port Delivery System for Sustained Delivery of Ranibizumab in Patients With Subfoveal Neovascular Age-Related Macular Degeneration **Phase II** – completed **Location:** US **Study completion date:** March 2019
Trial design	Randomized, parallel assignment, quadruple-blinded, active-controlled
Population	N=238; 50 years and older; newly diagnosed with wet AMD within 9 months of screening visit; participant must have received at least 2 prior ITV anti-vascular endothelial growth factor (VEGF) injections; demonstrated response to prior ITV anti-VEGF treatment
Intervention(s)	Ranibizumab; PDS implant with ranibizumab 10mg/ml, 40mg/ml or 100mg/ml
Comparator(s)	Ranibizumab; 0.5mg monthly through intravitreal injection
Outcome(s)	Time Until a Participant First Requires the PDS Implant Refill According to Protocol-Defined Refill Criteria [Time Frame: Baseline up to approximately 38 months]

	See trial record for full list of other outcomes
Results (efficacy)	The median time to first required refill was 15.8 months for the PDS 100 mg/mL arm. At month 22 in the PDS 100 mg/mL and monthly ranibizumab 0.5 mg arms, respectively, the mean BCVA change from baseline was +2.9 and +2.7 letters. Mean central foveal thickness change from baseline excluding pigment epithelial detachment height was generally similar between the PDS 100 mg/mL and monthly ranibizumab 0.5 mg arms.[14]
Results (safety)	No dose related series adverse events were observed[14]

ESTIMATED COST

The cost of ranibizumab PDS is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Aflibercept solution for injection for treating wet age-related macular degeneration (TA 294). July 2013.
- NICE technology appraisal. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (TA155). May 2012.
- NICE technology appraisal. Guidance on the use of photodynamic therapy for age-related macular degeneration (TA68). September 2003.
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- NICE interventional procedures guidance. Radiotherapy for age-related macular degeneration (IPG49). March 2004.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthalmology (Adult). D12/S/a.

OTHER GUIDANCE

- Clinical Council for Eye Health Commissioning (CCEHC). System and Assurance Framework for Eye-Health (SAFE) - Age-related Macular Degeneration. March 2018.[15]

- European Society of Retina Specialists (EURETINA). Guidelines for the Management of Neovascular Age-Related Macular Degeneration. September 2014.[16]
- The College of Optometrists and The Royal College of Ophthalmologists. Commissioning better eye care: Age-related macular degeneration. November 2013.[17]

ADDITIONAL INFORMATION

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