Health Technology Briefing
August 2024

Bevacizumab gamma for treating neovascular age-related macular degeneration

Company/Developer	Outlook Therapeutics Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28885	NICE ID: 11792	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Bevacizumab gamma is in clinical development as an intravitreal injection (given through the white part of your eye known as vitreous) for the treatment of wet/neovascular age-related macular degeneration (nAMD). nAMD is a retinal condition that can cause deterioration of vision. nAMD can affect any part of your retina, a thin layer of tissue on the inside back wall of the eye. nAMD affects the middle of the vision in one or both eyes. The initial symptom of nAMD is usually blurred or distorted central vision. Other symptoms can include seeing straight lines as wavy, objects looking smaller than usual, changes in colour and hallucinations. If untreated, nAMD can progress to blindness. Other than off-label use, there are currently no licensed ophthalmic formulations of bevacizumab for the treatment of nAMD.

Bevacizumab gamma is a monoclonal antibody (type of protein) that targets and binds to the vascular endothelial growth factor (VEGF) a protein responsible for the development of new blood vessels. In nAMD there are very high levels of VEGF, the newly developed vessels are unlike normal vessels and easily bleed or leak blood constituents, resulting in distortion and scarring of the retina. Bevacizumab gamma works to stop VEGF by blocking its protein binding abilities and reducing new blood vessel development and vascular leakage. This will offer the first ophthalmic formulation of bevacizumab for the treatment of nAMD, administered through intravitreal injection.

Proposed Indication

Treatment of wet/neovascular age-related macular degeneration (nAMD).[4]

Technology

Description

Bevacizumab gamma (bevacizumab-vikg; ONS-5010; LYTENAVA) is a recombinant humanised IgG1 monoclonal antibody (mAb) for human vascular endothelial growth factor (VEGF). Bevacizumab gamma binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. Bevacizumab gamma is a human VEGF inhibitor that binds to all isoforms of VEGF-A, thereby preventing interaction with receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A, bevacizumab gamma suppresses endothelial cells proliferation, neovascularization, and vascular permeability. Inhibition of angiogenesis works to block the growth of abnormal blood vessels in the back of the eye.[5]

Bevacizumab gamma is in clinical development for the treatment of patients with nAMD. In the phase III clinical trials (NORSE EIGHT, NCT06190093; NORSE THREE, NCT04516278; NORSE TWO, NCT03834753) patients are administered 1.25mg bevacizumab gamma as an intravitreal injection.[4,6-8]

Key Innovation

AMD is the commonest cause of severe visual impairment in older adults in the developed world and the cause of about two-thirds of registrations of visual impairment or blindness in the UK.[9] Bevacizumab is more cost-effective as compared to some treatments. Despite being the most cost-effective treatment for AMD, bevacizumab is still not the standard of care in Europe. Existing treatments can lead to overspending without additional benefits.[10] NICE has determined that bevacizumab is just as safe and effective as other treatments for treating nAMD.[11] Bevacizumab gamma would be the first ophthalmic formulation of bevacizumab in the EU and UK for treating nAMD.

Regulatory & Development Status

Bevacizumab is currently marketed in the EU/UK in combination with other technologies for the following indications:[12]

- colon cancer
- rectum cancer
- breast cancer
- non-small cell lung cancer
- renal cell cancer
- epithelial ovarian cancer
- fallopian tube cancer
- peritoneal cancer
- cervical cancer

Bevacizumab gamma is not currently in clinical trials for any other indication.

Bevacizumab is currently in phase III development for branch retinal vein occlusion, and diabetic macular oedema.[13]

Patient Group

Disease Area and Clinical Need

AMD is the term applied to changes, without any other obvious precipitating cause, which occur in the central area of the retina (macula) in people aged 50 years and over. Neovascular AMD (wet AMD) is the development of new blood vessels in the choroid. The new vessels are unlike normal vessels and easily bleed or leak blood constituents, resulting in distortion and scarring of the retina.[14] Without treatment, vision may get worse. This can happen gradually over several years ("dry AMD"). Progression to the wet form of AMD happens in about 10-15% of AMD patients. It is called "wet" due to the development of leaky blood vessels that have grown to compensate for the functional problems created by the dry form of AMD. The excessive growth of these leaky blood vessels is called neovascularisation, which is why wet AMD is also called neovascular AMD (nAMD).[15,16] Any stage of dry AMD can turn into nAMD — but nAMD is always late stage.[17] The cause of AMD is unknown, but established risk factors include older age, smoking, a family history of AMD, and genetic factors. Symptoms of AMD include distortion of vision, where straight lines appear crooked or wavy; painless loss, or blurring, of central or near-central vision; a black or grey patch affecting the central field of vision (scotoma). Other symptoms include, difficulty reading, driving, or seeing fine detail; flickering or flashing lights; and visual hallucinations.

It is estimated that around 39,800 people develop nAMD in the UK each year.[18]AMD is the commonest cause of severe visual impairment in older adults in the developed world and the cause of about two-thirds of registrations of visual impairment or blindness in the UK. AMD is slightly more common in women than in men and may be less common in people with non-European ancestry compared with people with European ancestry. Roughly half of advanced AMD is due to nAMD.[9] In England (2022-23) there were 64,344 finished consultant episodes (FCE) and 63,549 admissions for degeneration of macula and posterior pole (ICD-10 code H35.3) which resulted in 63,578 day cases and 766 FCE bed days.[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommend the following anti-VEGF intravitreal injection treatment options for nAMD:

- Faricimab [22]
- Brolucizumab [23]
- Aflibercept [20,21]
- Ranibizumab [20,21]
- Bevacizumab (off-label use) [11,20,21]

Clinical Trial Information

Trial	**NORSE EIGHT;** NCT06190093; Safety and effectiveness of bevacizumab gamma compared to Lucentis® in subjects with neovascular age-related macular degeneration **Phase III** – Recruiting **Location** – USA **Primary completion date**: September 2024
Trial Design	Randomised, parallel assignment, triple masking
Population	N = 400 (estimated); aged 50 years and older; adults with active primary subfoveal choroidal neovascularisation lesions secondary to AMD in the study eye
Intervention(s)	1.25mg bevacizumab gamma administered through intravitreal injection

Comparator(s)	0.5mg ranibizumab (Lucentis®) administered through intravitreal injection
Outcome(s)	**Primary outcome measure:** Evaluate the effectiveness of intravitreal injections of bevacizumab gamma compared to ranibizumab in preventing vision loss, as measured by the mean change in best corrected visual acuity (BCVA) at Week 8
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**NORSE THREE**; NCT04516278; A 3-month study to assess the safety of bevacizumab gamma in subjects with visual impairment due to retinal disorders **Phase III** – Completed **Location** – USA **Study completion date:** February 2021
Trial Design	Single group assignment, open label
Population	N = 195 (actual); aged 18 years and older; adults with active clinical diagnosis of one of the following retinal disorders: exudative AMD, diabetic macular oedema or branch retinal vein occlusion and, in the opinion of the Investigator, requires treatment with an anti-VEGF therapy
Intervention(s)	1.25mg bevacizumab gamma administered through intravitreal injection
Comparator(s)	0.5mg ranibizumab administered through intravitreal injection
Outcome(s)	**Primary outcome measure:** Frequency and incidence of treatment-emergent adverse events [Time Frame: 3 months]
Results (efficacy)	-
Results (safety)	Data from NORSE THREE indicated that in this study bevacizumab gamma showed no intraocular inflammation or vasculitis, and the frequency and incidence of adverse events and ocular adverse events were low. The most common adverse event in the study eye was conjunctival haemorrhage related to injection procedure, not to bevacizumab gamma, and there were no additional serious adverse events associated with these injections. NORSE THREE showed no unanticipated safety signals.[24]

Clinical Trial Information	
Trial	**NORSE TWO; NCT03834753**; A clinical effectiveness, multicentre, randomised, double-masked, controlled study of the efficacy and safety of bevacizumab gamma in subjects with subfoveal choroidal neovascularisation (CNV) secondary to age-related macular degeneration **Phase III** – Completed

	Location – USA **Study completion date**: July 2021
Trial Design	Randomised, parallel assignment, double blinded, active comparator
Population	N = 228 (actual); aged 50 years and older; adults with active primary subfoveal choroidal neovascularisation lesions secondary to AMD in the study eye
Intervention(s)	1.25mg bevacizumab gamma administered through intravitreal injection
Comparator(s)	0.5mg ranibizumab administered through intravitreal injection
Outcome(s)	**Primary outcome measure:** Proportion of subjects who gain 15 or more letters in BCVA. BCVA to be assessed as letters read using the Early Treatment Diabetic Retinopathy Study charts. A positive change represents an improvement in visual acuity. [Time Frame: Baseline, 11 months] See trial record for full list of other outcomes.
Results (efficacy)	• Top-line data from NORSE TWO showed that bevacizumab met the primary and key secondary endpoint for efficacy with clinically impactful change observed for treated patients. The primary endpoint difference in proportion of subjects gaining at least 15 letters BCVA was met and was highly statistically significant and clinically relevant. • In the intent-to-treat primary dataset, the percentage of patients who gained at least 15 letters who were treated with ranibizumab was 23%, and the percentage of patients who gained at least 15 letters who were treated with bevacizumab was 41% (p = 0.0052). The primary endpoint was also statistically significant and clinically relevant in the secondary per-protocol dataset (p = 0.04) where the percentages were almost identical, at 24% with ranibizumab and 41% with bevacizumab-vikg.[25]
Results (safety)	• In NORSE TWO, there was only a single related ocular serious adverse event reported in the bevacizumab trial arm, which resolved, and no unanticipated safety signals were detected. • The most common ocular adverse event was intravitreal injection-related haemorrhage in the tissues on the surface of the eye (conjunctival haemorrhage) that resolved without any sequela.[25]

Estimated Cost

The cost of bevacizumab gamma is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Faricimab for treating wet age-related macular degeneration (TA800). June 2022.
- NICE technology appraisal. Brolucizumab for treating wet age-related macular degeneration (TA672). February 2021.

- NICE technology appraisal. Aflibercept solution for injection for treating wet age-related macular degeneration (TA294). July 2013.
- NICE technology appraisal. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (TA155). May 2012.
- NICE guideline. Age-related macular degeneration (NG82). January 2018.
- NICE quality standard. Serious eye disorders (QS180). February 2019.
- NICE interventional procedures guidance. Epiretinal brachytherapy for wet age-related macular degeneration (IPG415). December 2011.
- NICE interventional procedures guidance. Limited translocation for wet age-related macular degeneration (IPG339). May 2010.
- NICE interventional procedures guidance. Macular translocation with 360° retinotomy for wet age-related macular degeneration (IPG340). May 2010.

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- The Royal College of Ophthalmologists. Age Related Macular Degeneration Services: Recommendations. 2024.[26]
- The Royal College of Ophthalmologists. Age Related Macular Degeneration Services: Evidence Base. 2024.[27]
- The Royal College of Ophthalmologists. New guidance for commissioning age related macular degeneration services. 2021.[28]
- American Academy of Ophthalmology. Age-related macular degeneration preferred practice pattern. 2019.[29]
- European Society of Retina Specialists. Guidelines for the management of neovascular age-related macular degeneration. 2014.[30]

Additional Information

Outlook Therapeutics Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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