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Newcastle University

Health Technology Briefing
September 2022

ONS-5010 for 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 avilable

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

ONS-5010 is an ophthalmic formulation of bevacizumab under development to be administered as an intravitreal injection for the treatment of wet/neovascular age-related macular degeneration (nAMD). nAMD is a retinal condition that can cause deterioration of vision. nAMD affects the middle of the vision in one or both eyes, and often initially presents with blurred or distorted central vision, but symptoms can also include seeing straight lines as wavy, objects looking smaller than usual, changes in colours, hallucinations and if untreated can progress to blindness. Despite high off-label use, there are currently no licenced ophthalmic formulations of bevacizumab for the treatment of nAMD.

Bevacizumab is a type of protein that binds to a growth factor responsible for the promotion of abnormal new blood vessels and promotes leakage from these vessels, leading to retinal oedema and haemorrhage. In nAMD, there are abnormally high levels of this growth factor, therefore, once ONS-5010 is administered, it prevents the binding of the growth factor to a specific protein on the cell surface, reducing cell proliferation, vascular leakage, and new blood vessel formation in the retina, resulting in decreased loss of vision. If licenced, ONS-5010 will offer the first ophthalmic formulation of bevacizumab for the treatment of nAMD, administered through intravitreal injection.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

Treatment of wet/neovascular age-related macular degeneration (nAMD).[1,2]

Technology

Description

ONS-5010 (LYTENAVA™, bevacizumab-vikg) is an investigational ophthalmic formulation of bevacizumab under development to be administered as an intravitreal injection for the treatment of nAMD. ONS-5010 is a recombinant humanized monoclonal antibody (mAb) that selectively binds with high affinity to all isoforms of human vascular endothelial growth factor (VEGF). This binding neutralises VEGF's biologic activity through a steric blocking of the binding of VEGF to its receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells. VEGF is a protein that promotes the growth of abnormal new blood vessels and promotes leakage from these vessels, leading to retinal oedema and haemorrhage. With nAMD, abnormally high levels of VEGF are secreted in the eye and lead to loss of vision. Following intravitreal injection, the binding of ONS-5010 to VEGF prevents the interaction of VEGF with its receptors on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation in the retina, resulting in decreased loss of vision.[3,4]

ONS-5010 is currently in clinical development. In phase III clinical trials (NCT03834753, NCT04516278, NCT03844074), 1.25mg ONS-5010 is administered through intravitreal injection.[1,2,5]

Key Innovation

There are currently no approved ophthalmic formulations of bevacizumab, leading to off-label use of the drug to treat retinal diseases, including nAMD.[6] Off-label drug use can lead to preventable adverse drug events, poorer product quality and discrepant product information or labelling.[7]

If licenced, ONS-5010 will offer the first ophthalmic formulation of bevacizumab for the treatment of nAMD, administered through intravitreal injection.

Regulatory & Development Status

ONS-5010 does not currently have Marketing Authorisation in the UK/EU for any indication. Bevacizumab in combination with other medicinal products, currently has Marketing Authorisation as systemic therapy for a number of cancer indications.[8]

ONS-5010 is currently in phase III clinical trials for treatment of retinal disorders.[9]

Patient Group

Disease Area and Clinical Need

AMD is a common condition that affects the middle part of the vision, most often occurring in people aged 50-70. Without treatment it causes deterioration in vision, this can happen gradually over years (dry AMD), or over a few weeks or months (wet AMD).[10] Wet AMD is also referred to as nAMD. The retina is a layer of neurosensory tissue in the eye that converts light into neural signals that the brain interprets as images. The macula is the part of the retina that contains the highest concentration of cones, which are essential for central vision. In nAMD, VEGF drives the development of choroidal neovascularization (CNV), where new vessels grow under or through the retinal pigment epithelium (RPE) via breaks in the Bruch membrane.

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This may lead to bleeding under the retina, detachment or atrophy of the RPE, or sub-retinal or sub-RPE fluid accumulation with associated vision loss.[11] nAMD affects the middle of the vision in one or both eyes, and the first symptom is often blurred or distorted central vision. Other symptoms can also include: seeing straight lines as wavy; objects looking smaller than usual; changes in colours; hallucinations and if untreated can progress to blindness.[12] The exact cause of nAMD is unknown but it has been linked to smoking, high blood pressure, being overweight, and having a family history of AMD.[10]

It is estimated that around 39,800 people develop nAMD in the UK each year.[13] A 2012 study estimated that the prevalence of nAMD in the UK is 1.2–6.3%.[14] Applying this figure to 2020 population estimates, it would be estimated that between 804,974 and 4,226,117 people have nAMD in the UK.[15] In England (2020-21), there were 52,204 finished consultant episodes (FCE) for degeneration of macula and posterior pole (ICD-10 code: H35.3), with 52,142 hospital admissions that resulted in 51,370 day cases and 746 FCE bed days.[16]

Recommended Treatment Options

NICE currently recommends the following treatment options for nAMD:[17-20]

- Faricimab
- Brolucizumab
- Aflibercept solution for injection
- Ranibizumab and pegaptanib

Clinical Trial Information

Trial	**NORSE TWO; NCT03834753;** A Clinical Effectiveness, Multicenter, Randomised, Double-masked, Controlled Study of the Efficacy and Safety of ONS-5010 in Subjects With Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration **Phase III** – completed **Location(s):** USA **Actual study completion date:** July 2021
Trial Design	Randomised, parallel assignment, double blinded, active comparator
Population	N=228; aged 50 years and older; active primary subfoveal choroidal neovascularization lesions secondary to AMD in the study eye
Intervention(s)	1.25mg ONS-5010 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 best corrected visual acuity (BCVA) [Time frame: Baseline, 11 months] See trial record for full list of other outcomes
Results (efficacy)	• Top-line data from NORSE TWO showed that ONS-5010 bevacizumab-vikg 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.

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	• In the intent-to-treat (ITT) 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-vikg was 41% (p = 0.0052). The primary endpoint was also statistically significant and clinically relevant in the secondary per-protocol (PP) dataset (p = 0.04) where the percentages were almost identical, at 24% with ranibizumab and 41% with bevacizumab-vikg.[21]
Results (safety)	• In NORSE TWO, there was only a single related ocular serious adverse event reported in the bevacizumab-vikg 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.[21]

Trial	**NORSE THREE;** NCT04516278; A 3-month Study to Assess the Safety of ONS-5010 in Subjects With Visual Impairment Due to Retinal Disorders **Phase III –** completed **Location(s):** USA **Actual study completion date:** February 2021
Trial Design	Single group assignment, open label
Population	N=195; aged 18 years and older; active clinical diagnosis of one of the following retinal disorders: exudative age-related macular degeneration (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 ONS-5010 administered by intravitreal injection
Comparator(s)	No comparator
Outcome(s)	Primary outcome: 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 ONS-5010 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 ONS-5010, and there were no additional serious adverse events associated with these injections. • NORSE THREE showed no unanticipated safety signals.[23]

Estimated Cost

The cost of ONS-5010 is not yet known.

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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. New guidance for commissioning age related macular degeneration services. 2021.[24]
- American Academy of Ophthalmology. Age-related macular degeneration preferred practice pattern. 2019.[25]
- European Society of Retina Specialists. Guidelines for the management of neovascular age-related macular degeneration. 2014.[26]

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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