

**NIHR Innovation Observatory
Evidence Briefing April 2017**

**Brolucizumab (ESBA1008; RTH258) for neovascular
age-related macular degeneration (nAMD)**

NIHRIO (HSRIC) ID: 10535

NICE ID: 8412

LAY SUMMARY

Age-related macular degeneration (AMD) is a major cause of visual impairment in older adults in the UK. It has three stages - early, intermediate, and late - and can occur in one or both eyes. It is possible for one eye to be at the early stage and the other at late stage. There are two types of late stage AMD: 'dry' AMD and 'wet' (or neovascular) AMD. One of the ways wet AMD can be treated is with injections of growth inhibitors delivered directly in to the eye (VEGF inhibitors). Brolucizumab is a new VEGF inhibitor, and if licensed, would offer another treatment option for patients with wet AMD. One of its potential benefits could be a potentially longer treatment effect duration, which would reduce the frequency of injections.

This briefing is based on information available at the time of research 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.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

- Neovascular age-related macular degeneration (nAMD); active, untreated

TECHNOLOGY

DESCRIPTION

Angiogenesis is a key aspect of nAMD.¹ Vascular endothelial growth factor-A (VEGF-A) promotes the growth of vascular endothelial cells and is a major mediator of angiogenesis and vascular leakage in nAMD.¹ Brolucizumab (DLX-1008; ESBA-1008; RTH-258) is a novel anti-VEGF agent for nAMD patients. Brolucizumab is a single chain antibody fragment that according to the manufacturer may be longer acting than approved treatments for nAMD, potentially enabling patients to go longer between treatments.²

Brolucizumab is delivered as an intravitreal injection, administered in a 6 mg/50µL dose in phase III trials. It is initially injected three times at four week intervals, followed by injections every 12 weeks unless there is disease activity as defined in the trial protocol (cf. Efficacy).

It does not currently have Marketing Authorisation in the EU for any indication.

Phase III trials for diabetic macular oedema are planned for brolucizumab.³

INNOVATION and/or ADVANTAGES

If licenced, brolucizumab will provide an additional treatment option for patients with nAMD.

DEVELOPER

Novartis Pharmaceuticals UK Limited (Alcon Eye Care UK Ltd)

PATIENT GROUP

BACKGROUND

Age-related macular degeneration (AMD) is the most common form of severe visual impairment in the developed world, in the UK alone accounting for over half of those certified as severely or partially sight-impaired.⁴

It is caused by changes related to ageing (not attributable to another cause) in the central area of the retina, the macula.⁵ It is a painless condition but eventually leads to the impairment of vision.⁵ Patients may present with difficulty in performing daily activities such as driving, reading and recognising faces.⁵

AMD is classified into early, intermediate or late stage of disease, and late AMD is further classified as either 'wet' AMD (neovascular/exudative; nAMD) or 'dry' AMD (advanced geographic atrophy).⁵ Neovascular AMD can develop very suddenly but can be treated if caught early – if left untreated, over half of patients will become visually impaired or blind within 3 years.⁵

CLINICAL NEED and BURDEN OF DISEASE

Neovascular AMD accounts for 10% of all cases of AMD and about 60% of advanced (late stage) cases of AMD.⁶ A 2012 Bayesian meta-analysis estimated the UK prevalence of nAMD to be 1.2% overall (95% credible interval: 0.9% to 1.7%), 2.5% in those aged ≥ 65 (95% credible interval: 1.8% to 3.4%) and 6.3% in those aged ≥ 80 (95% credible interval: 4.5% to 8.6%).⁷ The annual incidence of nAMD was 2.3 per 1,000 women and 1.4 in 1,000 men.⁷

In 2015 to 2016, there were 79,714 hospital admissions in England due to AMD (degeneration of the macula and posterior pole; ICD10: H35.3), with 79,997 finished consultant episodes and 1,974 bed days.⁸

PATIENT PATHWAY

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.
- NICE clinical guideline in development. Age-related macular degeneration: diagnosis and management (GID-CGWAVE0658). Publication expected in November 2017.
- NICE interventional procedures guidance. Miniature lens system implantation for advanced age-related macular degeneration (IPG565). September 2016.
- NICE interventional procedures guidance. Transpupillary thermotherapy for age-related macular degeneration (IPG58). May 2004.
- NICE interventional procedures guidance. Radiotherapy for age-related macular degeneration (IPG49). March 2004.

NHS ENGLAND and POLICY GUIDANCE

- UK Vision Strategy 2013–2018, <http://www.ukvisionstrategy.org.uk/>

OTHER GUIDANCE

- The Royal College of Ophthalmologists. Age-Related Macular Degeneration: Guidelines for Management. September 2013. <https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf>

- The Royal College of Optometrists and the Royal College of Ophthalmologists. Age-related macular degeneration. Commissioning better eye care - Clinical commissioning guidance. November 2013.
- European Society of Retina Specialists (EURETINA). Guidelines for the management of neovascular age-related macular degeneration. 2014.

CURRENT TREATMENT OPTIONS

The treatment options for nAMD include anti-angiogenic therapies, laser anticoagulation and photodynamic therapy.⁵

In addition, two other VEGF inhibitors, aflibercept (Eylea) injections and ranibizumab (Lucentis) injections, are already recommended by NICE for nAMD.^{9 10}

EFFICACY and SAFETY

Trial	HAWK; RTH258 (two arms for different doses) versus Aflibercept; NCT02307682; phase III
Sponsor	Alcon Research
Status	ongoing
Source of Information	Trial registry, ¹¹ Pharmaprojects
Location	US, Canada, Australia, Israel and other countries
Design	Randomised, active-controlled
Participants	N=1,600; aged ≥50; subjects with untreated active choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye.
Schedule	RTH258 solution for intravitreal injection, (two arms: 3mg or 6mg/50µL dose), single injection at Day 0, Week 4, and Week 8, then as specified in the protocol up to Week 92. Comparator: Aflibercept 2mg/50µL dose, same schedule
Follow-up	96 weeks
Primary Outcomes	Change in best corrected visual acuity (BCVA) from baseline at week 48
Secondary Outcomes	Average change in BCVA from baseline, proportion of patients with positive q12 treatment status
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Final data collection date for primary outcome measure reported as May 2017.

Trial	HARRIER; RTH258 Versus Aflibercept; NCT02434328; phase III
Sponsor	Alcon Research
Status	ongoing
Source of Information	Trial registry ¹²
Location	EU (incl UK), Taiwan, Russia and other countries
Design	Randomised, active-controlled
Participants	N=1,200; aged ≥50; untreated active choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye
Schedule	RTH258 solution for intravitreal injection, 6mg/50µL dose, single injection at Day 0, Week 4, and Week 8, then as specified in the protocol up to Week 92. Comparator: Aflibercept 2mg/50µL dose, same schedule
Follow-up	96 weeks
Primary Outcomes	Change in best corrected visual acuity (BCVA) from baseline at week 48
Secondary Outcomes	Average change in BCVA from baseline, proportion of patients with positive q12 treatment status
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Final data collection date for primary outcome measure reported as June 2017.

Trial	OSPREY; ESBA1008 Versus EYLEA; NCT01796964; C-12-006; phase II
Sponsor	Alcon Research
Status	Complete (published in abstract)
Source of Information	Trial registry, ¹³ publication abstracts, ^{14 15} Pharmaprojects
Location	USA
Design	Randomised, active-controlled
Participants	N=173; aged ≥50; Diagnosis of wet age-related macular degeneration
Schedule	Active Comparator: Aflibercept (Eylea) Active intravitreal (IVT) injections at baseline with 2 additional loading doses of the assigned investigational product at 4-week intervals (ie, at Weeks 4 and 8) and then received further injections at 8-weeks intervals at Weeks 16, 24, and 32. Subjects in the ESBA1008 group also received an injection at Week 44, while subjects in the EYLEA group also received injections at Weeks 40 and 48. To maintain the study masking, subjects in the ESBA1008 group received sham

	injections at Weeks 40 and 48 (when the subjects in the EYLEA group received active injections), while subjects in the EYLEA group received a sham injection at Week 44 (when the subjects in the ESBA1008 group received an active injection).
Follow-up	56 weeks
Primary Outcomes	Best-Corrected Visual Acuity (BCVA) Change From Baseline (No. of Letters) to Week 12
Secondary Outcomes	BCVA Change From Baseline (No. of Letters) to Week 16 and at other timepoints, Central Subfield Thickness
Key Results	<p>Full Analysis n=89. Mean age 78.0 (range 55.0-96.0 years). Non-inferiority was met, and RTH258 was well tolerated.</p> <p>C-12-006 [n = 89; RTH258 6.0 (n = 44), aflibercept 2.0 (n = 45) mg] demonstrated BCVA noninferiority at weeks 12 (P = 0.63) and 16 (P = 0.81) and successful Q12 treatment in ~50% of RTH258 patients with no new safety concerns for both.</p> <p>Visual acuity gains were non-inferior to aflibercept, with numerically greater reduction and rapid improvement in abnormal retinal fluid observed in brolocizumab-treated patients.</p> <p>Patients treated every 3 mth with brolocizumab also experienced a prolonged duration-of-action, leading to a reduced treatment burden.</p>
Adverse effects (AEs)	Both brolocizumab and aflibercept were well tolerated and no new safety signal was reported during the study.
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of brolocizumab is not yet known.

A NICE scoping document notes that one of the current treatment options, ranibizumab, has a very significant cost. In 2013/14 ranibizumab was the second most expensive medicine positively appraised by NICE, and in the same year cost the NHS £244 million (although some of this cost was for other licensed indications).⁵

Costs listed in BNF for ranibizumab¹⁶ and aflibercept¹⁷ are:

- Eylea 2mg/50microlitres solution for injection vials (Bayer Plc); Aflibercept 40 mg per 1 ml, 1 vial NHS indicative price = £816.00
- Lucentis 1.65mg/0.165ml solution for injection pre-filled syringes (Novartis Pharmaceuticals UK Ltd); Ranibizumab 10 mg per 1 ml, 1 pre-filled disposable injection NHS indicative price = £551.00

Both Eylea and Lucentis have confidential Patient Access Scheme agreements in place; the above figures do not therefore represent actual NHS costs.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

- | | |
|--|---|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input type="checkbox"/> Reduced symptoms or disability |
| <input checked="" type="checkbox"/> Other: <i>improved patient convenience (potentially longer duration of action)</i> | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|--|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|--|--|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input checked="" type="checkbox"/> Other reduction in costs: <i>reduced care visits (potentially longer duration of action)</i> |
| <input type="checkbox"/> Other: <i>specify, e.g. uncertain unit cost compared to existing treatments</i> | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified: <i>specify</i> | <input checked="" type="checkbox"/> None identified |
|---|---|

REFERENCES

¹ Mitchell, P. A systematic review of the efficacy and safety outcomes of anti-VEGF agents used for treating neovascular age-related macular degeneration: comparison of ranibizumab and bevacizumab. *Current medical research and opinion*, 2011, 27(7), pp. 1465-1475.

² Novartis. *Annual Report 2016*. Available from: <https://www.novartis.com/sites/www.novartis.com/files/novartis-annual-report-2016-en.pdf> [Accessed 6 April 2017]

³ Pharmaprojects. Brolucizumab. [Accessed 6 April 2017, log-in required]

-
- ⁴ Hill, D., 2015. Age-related macular degeneration. *InnovAIT: Education and inspiration for general practice*, 8 (7): 425-430
- ⁵ NICE guideline scope. *Age-related macular degeneration: diagnosis and management*. October 2015 <https://www.nice.org.uk/guidance/GID-CGWAVE0658/documents/final-scope> Accessed 6 April 2017
- ⁶ Patient Info. *Age-related Macular Degeneration* Available from: <https://patient.info/doctor/age-related-macular-degeneration-pro> [Accessed 6 April 2017]
- ⁷ Owen, C.G., Jarrar, Z., Wormald, R., Cook, D.G., Fletcher, A.E. and Rudnicka, A.R. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *British Journal of Ophthalmology*, 2012, 96: 752-756.
- ⁸ NHS Digital. *Hospital Admitted Patient Care Activity, 2015-16*. Available from: <http://www.content.digital.nhs.uk/catalogue/PUB22378> [Accessed 28 March 2017]
- ⁹ NICE technology appraisal guidance (TA294). *Aflibercept solution for injection for treating wet age -related macular degeneration*. July 2013 <https://www.nice.org.uk/guidance/TA294/> [Accessed 6 April 2017]
- ¹⁰ NICE technology appraisal guidance (TA 155). *Ranibizumab and pegaptanib for the treatment of age-related macular degeneration*. Updated May 2012. <https://www.nice.org.uk/guidance/ta155> [Accessed 6 April 2017]
- ¹¹ ClinicalTrials.gov. *Efficacy and Safety of RTH258 Versus Aflibercept*. Available from: <https://clinicaltrials.gov/show/NCT02307682> [Accessed 6 April 2017]
- ¹² ClinicalTrials.gov. *Efficacy and Safety of RTH258 Versus Aflibercept - Study 2*. Available from: <https://clinicaltrials.gov/show/NCT02434328> [Accessed 6 April 2017]
- ¹³ ClinicalTrials.gov. *Efficacy and Safety Study of ESBA1008 Versus EYLEA*. Available from: <https://clinicaltrials.gov/show/NCT01796964> [Accessed 6 April 2017]
- ¹⁴ Singerman, L.J., Weichselberger, A. and Sallstig, P., 2015. OSPREY trial: randomized, active-controlled, phase II study to evaluate safety and efficacy of RTH258, a humanized single-chain anti-VEGF antibody fragment, in patients with neovascular AMD. *Investigative Ophthalmology & Visual Science*, 56(7), pp.4801-4801.
- ¹⁵ Chen, J.-T. (2016) Study Design of an Innovative Phase III, Two-Year, Randomized, Double-Masked, Multicenter, Two-Arm Study Comparing the Efficacy and Safety of RTH258 6 mg Versus Aflibercept in Subjects With Neovascular Age-Related Macular Degeneration, APAO Congress, Poster No.: EX2-273. Available from: <http://2016.apaophth.org/wp-content/uploads/2016/02/Abstract-Book.pdf>
- ¹⁶ BNF. *Ranibizumab*. Available from: <https://www.medicinescomplete.com/mc/bnf/current/PHP7169-ranibizumab.htm#PHP7169-medicinalForms> [Accessed 6 April 2017]
- ¹⁷ BNF. *Aflibercept*. Available from: https://www.medicinescomplete.com/mc/bnf/current/PHP33788-aflibercept.htm?q=aflibercept&t=search&ss=text&tot=6&p=1#_hit [Accessed 6 April 2017]