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

NIHRIO (HSRIC) ID: 10535  NICE ID: 8412

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.

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TARGET GROUP

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

TECHNOLOGY

DESCRIPTION

Angiogenesis is a key aspect of nAMD. 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. 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.

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.

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.

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

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). 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.
Neovascular AMD accounts for 10% of all cases of AMD and about 60% of advanced (late stage) cases of AMD. 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%). The annual incidence of nAMD was 2.3 per 1,000 women and 1.4 in 1,000 men.

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.

### PATIENT PATHWAY

#### RELEVANT GUIDANCE

#### NICE GUIDANCE


#### NHS ENGLAND and POLICY GUIDANCE


#### OTHER GUIDANCE

• 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>HAWK; RTH258 (two arms for different doses) versus Aflibercept; NCT02307682; phase III</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Alcon Research</td>
</tr>
<tr>
<td>Status</td>
<td>ongoing</td>
</tr>
<tr>
<td>Source of Information</td>
<td>Trial registry,(^11) Pharmaprojects</td>
</tr>
<tr>
<td>Location</td>
<td>US, Canada, Australia, Israel and other countries</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled</td>
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<tr>
<td>Participants</td>
<td>N=1,600; aged ≥50; subjects with untreated active choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye.</td>
</tr>
<tr>
<td>Schedule</td>
<td>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</td>
</tr>
<tr>
<td>Follow-up</td>
<td>96 weeks</td>
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<tr>
<td>Primary Outcomes</td>
<td>Change in best corrected visual acuity (BCVA) from baseline at week 48</td>
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<tr>
<td>Secondary Outcomes</td>
<td>Average change in BCVA from baseline, proportion of patients with positive q12 treatment status</td>
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<tr>
<td>Key Results</td>
<td>-</td>
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<tr>
<td>Adverse effects (AEs)</td>
<td>-</td>
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<tr>
<td>Expected reporting date</td>
<td>Final data collection date for primary outcome measure reported as May 2017.</td>
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</table>
### Trial: HARRIER; RTH258 Versus Aflibercept; NCT02434328; phase III

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<thead>
<tr>
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<tr>
<td>Status</td>
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<tr>
<td>Source of Information</td>
<td>Trial registry[^12]</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), Taiwan, Russia and other countries</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled</td>
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<tr>
<td>Participants</td>
<td>N=1,200; aged ≥50; untreated active choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye</td>
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<tr>
<td>Schedule</td>
<td>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</td>
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<tr>
<td>Expected reporting date</td>
<td>Final data collection date for primary outcome measure reported as June 2017.</td>
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</table>

### Trial: OSPREY; ESBA1008 Versus EYLEA; NCT01796964; C-12-006; phase II

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<th>Sponsor</th>
<th>Alcon Research</th>
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<tr>
<td>Status</td>
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<tr>
<td>Source of Information</td>
<td>Trial registry[^13], publication abstracts[^14][^15], Pharmaprojects</td>
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<tr>
<td>Location</td>
<td>USA</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled</td>
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<tr>
<td>Participants</td>
<td>N=173; aged ≥50; Diagnosis of wet age-related macular degeneration</td>
</tr>
<tr>
<td>Schedule</td>
<td>Active Comparator: Aflibercept (Eylea)</td>
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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**
Full Analysis n=89. Mean age 78.0 (range 55.0-96.0 years). Non-inferiority was met, and RTH258 was well tolerated.

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.

Visual acuity gains were non-inferior to aflibercept, with numerically greater reduction and rapid improvement in abnormal retinal fluid observed in brolucizumab-treated patients.

Patients treated every 3 mth with brolucizumab also experienced a prolonged duration-of-action, leading to a reduced treatment burden.

**Adverse effects (AEs)**
Both brolucizumab and aflibercept were well tolerated and no new safety signal was reported during the study.

**Expected reporting date**
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**ESTIMATED COST and IMPACT**

**COST**

The cost of brolucizumab 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

- [x] Reduced mortality/increased length of survival
- [ ] Reduced symptoms or disability
- [x] Other: improved patient convenience (potentially longer duration of action)
- [ ] No impact identified

#### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- [ ] Increased use of existing services
- [x] Decreased use of existing services
- [ ] Re-organisation of existing services
- [ ] Need for new services
- [ ] Other
- [ ] None identified

#### IMPACT ON COSTS and OTHER RESOURCE USE

- [ ] Increased drug treatment costs
- [ ] Reduced drug treatment costs
- [ ] Other increase in costs
- [x] Other reduction in costs: reduced care visits (potentially longer duration of action)
- [ ] Other: specify, e.g. uncertain unit cost compared to existing treatments
- [ ] None identified

#### OTHER ISSUES

- [ ] Clinical uncertainty or other research question identified: specify
- [x] None identified

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### REFERENCES


