NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
August 2022

High dose aflibercept for treating neovascular age-related macular degeneration (nAMD)

Company/Developer	Bayer AG

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28525	NICE TSID: 10590	UKPS ID: 659585

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

High dose aflibercept is in development for the treatment of neovascular age-related macular degeneration (nAMD). nAMD is a condition that commonly affects people over the age of 50 and causes vision disturbance or blind spots in the centre of the visual field and progresses rapidly over several weeks or months without any treatment. Aflibercept is licensed at a lower concentration for the treatment for nAMD but the more concentrated high-dose version is expected to increase the time needed between doses while retaining the effectiveness in preventing further damage to vision.

Aflibercept has been designed to attach to and block the effects of a protein called vascular endothelial growth factor A (VEGF-A) that causes abnormal growth of blood vessels in the back of the eye. By blocking the activity of this protein, aflibercept reduces the growth of abnormal blood vessels, and controls leakage and swelling. High dose aflibercept is administered via injection into the eye in patients with untreated nAMD. If licenced aflibercept will offer a new treatment option for patients with nAMD.

Proposed Indication

Treatment of neovascular age-related macular degeneration (nAMD).[1]

Technology

Description

Aflibercept (Eylea, BAY86-5321) is an engineered protein that has been designed to attach to and block the effects of a substance called vascular endothelial growth factor A (VEGF-A) and can also attach to other proteins such as placental growth factor (PIGF). VEGF-A and PIGF are involved in stimulating the abnormal growth of blood vessels in patients with AMD, certain types of macular oedema and myopic choroidal neovascularisation. By blocking these factors, aflibercept reduces the growth of the blood vessels and controls the leakage and swelling.[2]

In the phase III study (NCT04423718) high-dose (8mg) aflibercept will be administered via intravitreal (IVT) injection to treatment naïve patients with nAMD, with doses occurring in 12 or 16 week intervals.[3]

Key Innovation

Eyes treated with high dose aflibercept (8mg compared to the already licensed 2mg) were more likely to be dry in the centre and were seen to have a 7.9 average letter improvement from baseline compared to 5.1 letters for standard aflibercept. 40% of patients treated with aflibercept 8 mg did not have fluid in the centre subfield compared to 28% of patients treated with aflibercept 2mg. Twice as many patients treated with aflibercept 8 mg had no macular fluid compared to patients treated with aflibercept 2mg. The new concentrated high-dose aflibercept formulation enables a greater amount of medicine to be administered with each treatment, and could potentially extend the time between doses while retaining the efficacy and safety profile seen with 2mg aflibercept.[4]

Regulatory & Development Status

Aflibercept has Marketing Authorisation in the UK for the treatment of adult patients with:[5]

- nAMD
- Visual impairment due to macular oedema secondary to retinal vein occlusion
- Visual impairment due to diabetic macular oedema (DME)
- Visual impairment due to myopic choroidal neovascularisation (CNV)

Aflibercept is in phase III/ II clinical development for:[6]

- Retinopathy of prematurity
- Radiation retinopathy
- Uveal melanoma
- Colorectal cancer
- Thyroid eye disease
- Polypoid choroidal vasculopathy

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).[7] 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 which may lead to bleeding under the retina, detachment or atrophy of the retinal pigment epithelium (RPE), or sub-retinal or sub-RPE fluid accumulation with associated vision loss.[8] 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.[9] 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.[7]

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. Estimates indicate that around 39,800 people develop nAMD in the UK each year; given a total UK population of 60 million, this equates to 663 new cases per million per year.[10] 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.[11]

Recommended Treatment Options

NICE recommended treatments for nAMD include injections into the eye with anti-VEGF medicines such as faricimab, brolucizumab, or aflibercept every 1-3 months for as long as needed. If injections alone are not affective then procedures such as photodynamic therapy may also be used concurrently.[12,13]

Clinical Trial Information

Trial	**CANDELA; NCT04126317;** A Randomized, Single-Masked, Active-Controlled Phase 2 Study of the Safety, Tolerability, and Efficacy of Repeated Doses of High-Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration **Phase II** – Completed **Location(s):** USA and Puerto Rico **Study completion date:** November 2021
Trial Design	Randomised, parallel assignment, single-masked, active-controlled
Population	N= 106; Treatment-naïve subjects with active subfoveal choroidal neovascularization (CNV) secondary to nAMD; aged 50 years and older.
Intervention(s)	High dose aflibercept, intravitreal (IVT) administration
Comparator(s)	Aflibercept, IVT administration
Outcome(s)	Primary outcome measures:

	• Incidence of treatment-emergent adverse events [Time Frame: Up to Week 4] • Incidence of serious adverse events (SAEs) [Time Frame: Up to Week 4] • Proportion of patients without retinal fluid in the centre subfield [Time Frame: At week 16]
Results (efficacy)	Patients treated with aflibercept 8 mg had no retinal fluid at week 16, when the primary efficacy endpoint was assessed. At this timepoint, 43% (n=23/53) had no fluid in the macula compared to 26% for EYLEA (n=14/53) (p=0.0667); and 51% (n=27) had no fluid in the centre subfield compared to 34% for EYLEA (n=18) (p=0.0770). At week 16, patients in both treatment groups had received three initial doses (administered at weeks 0, 4 and 8), after which dosing was extended to every 12 weeks. Aflibercept 8 mg continued to show numeric improvements in anatomical and vision outcomes compared to EYLEA through 44 weeks.[4]
Results (safety)	Through 44 weeks, adverse events (AEs) in the study eye occurred in 38% (n=20/53) of both aflibercept 8 mg and EYLEA patients. There were no serious AEs of intraocular inflammation (including occlusive retinal vasculitis), and no anti-platelet trialists' collaboration (APTC)-defined arterial thromboembolic events. The most common ocular AEs that occurred more frequently in the aflibercept 8 mg group were vitreous detachment (4 aflibercept 8 mg, 2 EYLEA), conjunctival haemorrhage (3 aflibercept 8 mg, 2 EYLEA) and retinal tear (2 aflibercept 8 mg, 0 EYLEA). There was one patient death in the aflibercept 8 mg unrelated to treatment.[4]

Trial	**PULSAR; NCT04423718, 2019-003851-12;** Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration **Phase III-** Active, not recruiting **Location(s):** 12 EU countries, USA, Canada, and other countries **Primary completion date:** July 2022
Trial Design	Randomised, parallel assignment, quadruple-masked, active-controlled
Population	N= 1016; Subjects with active subfoveal CNV secondary to nAMD; aged 50 years and older.
Intervention(s)	High-dose aflibercept, IVT administration
Comparator(s)	Aflibercept (2mg), IVT administration
Outcome(s)	Primary Outcome Measure: • Change in best corrected visual acuity (BCVA) measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score [Time Frame: At baseline and week 48] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The hospital indicative price for aflibercept (40mg per 1ml) is £816.00 per vial/pre-filled syringe.[14] The cost of high-dose aflibercept is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Ranibizumab port delivery system for treating wet age-related macular degeneration (ID3983) [GID-TA10879]. Expected date of issue to be confirmed.
- 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.[15]
- American Academy of Ophthalmology. Age-related macular degeneration preferred practice pattern. 2019.[16]
- European Society of Retina Specialists. Guidelines for the management of neovascular age-related macular degeneration. 2014.[17]
- The Royal College of Ophthalmologists. Age-related macular degeneration guidelines for management. 2013.[18]

Additional Information

References

1 ClinicalTrials.gov. *Study to Gather Information on Safety and Use of High Dose Aflibercept Injection Into the Eye in Patients With an Age Related Eye Disorder That Causes Blurred Vision or a Blind Spot Due to Abnormal Blood Vessels That Leak Fluid Into the Light Sensitive Lining Inside the Eye (PULSAR)*. *Trial ID: NCT04423718*. 2022. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04423718 [Accessed July 7th, 2022].

2 European Medicines Agency (EMA). *Eylea: Aflibercept.* 2022. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/eylea [Accessed July 12th, 2022].

3 EU Clinical Trials Register. *Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients With Neovascular Age-Related Macular Degeneration*. *Trial ID: 2019-003851-12*. 2020. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2019-003851-12 [Accessed July 19th, 2022].

4 Regeneron. *REGENERON PRESENTS ENCOURAGING PHASE 2 RESULTS FOR HIGH-DOSE AFLIBERCEPT 8 MG IN WET AGE-RELATED MACULAR DEGENERATION AT ANGIOGENESIS MEETING.* 2022. Available from: https://investor.regeneron.com/news-releases/news-release-details/regeneron-presents-encouraging-phase-2-results-high-dose [Accessed July 7th, 2022].

5 Electronic Medicines Compendium (EMC). *Eylea 40mg/ml solution for injection in a vial.* 2021. Available from: https://www.medicines.org.uk/emc/product/2879/smpc#gref [Accessed July 7th, 2022].

6 ClinicalTrials.gov. *47 Studies found for: eylea | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Interventional Studies | Phase 2, 3 | Industry.* 2022. Available from: https://www.clinicaltrials.gov/ct2/results?term=eylea&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=Intr&rslt=&phase=1&phase=2&fund=2&Search=Apply [Accessed July 7th, 2022].

7 National Health Service (NHS). *What is AMD?* 2021. Available from: https://www.nhs.uk/conditions/age-related-macular-degeneration-amd/ [Accessed July 12th, 2022].

8 Hobbs SD, Pierce K. *Wet Age-Related Macular Degeneration (Wet AMD).* 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572147/ [Accessed July 12th, 2022].

9 National Health Service (NHS). *Age-related macular degeneration: Symptoms.* 2021. Available from: https://www.nhs.uk/conditions/age-related-macular-degeneration-amd/symptoms/ [Accessed July 12th, 2022].

10 National Institute for Health and Care Excellence (NICE). *Age-related macular degeneration: NICE guideline [NG82].* 2018. Available from: https://www.nice.org.uk/guidance/ng82/chapter/Context [Accessed July 12th, 2022].

11 National Health Service (NHS) Digital Office for National Statistics. *Hospital Admitted Patient Care Activity, 2020-21: Diagnosis.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21#chapter-index [Accessed February 10th, 2022].

12 National Health Service (NHS). *Treatments: Age-related macular degeneration (AMD).* 2021. Available from: https://www.nhs.uk/conditions/age-related-macular-degeneration-amd/treatment/ [Accessed July 11th, 2022].

13 National Institute for Health and Care Excellence (NICE). *30 results for wet age related macular degeneration.* 2022. Available from: https://www.nice.org.uk/search?q=wet+age+related+macular+degeneration [Accessed July 11th, 2022].

14 British National Formulary (BNF). *Aflibercept- Medicinal forms.* 2022. Available from: https://bnf.nice.org.uk/drugs/aflibercept/medicinal-forms/ [Accessed July 7th, 2022].

15 The Royal College of Ophthalmologists. *New Guidance for Commissioning Age Related Macular Degeneration Services.* 2021. Available from: https://www.rcophth.ac.uk/news-views/amd-commissioning-guidance-2021/ [Accessed July 7th, 2022].

16 American Academy of Ophthalmology. *Age-related macular degeneration preferred practice pattern.* 2019. Available from: https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp [Accessed July 7th, 2022].

17 European Society of Retina Specialists. Guidelines for the management of neovascular age-related macular degeneration. *British Journal of Ophthalmology*. 2014;98:1144-67. Available from: https://bjo.bmj.com/content/98/9/1144.info.

18 The Royal College of Ophthamologists. *Age-Related Macular Degeneration: Guidelines for Management.* 2013. Available from: http://bmec.swbh.nhs.uk/wp-content/uploads/2013/03/RCOphth-ARMD-Management-September-2013.pdf [Accessed July 7th, 2022].

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