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Newcastle University

Health Technology Briefing
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Avacincaptad pegol for the treatment of geographic atrophy secondary to age-related macular degeneration

Company/Developer	Astellas Pharma Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 12113	NICE ID: Not available	UKPS ID: 671969

Licensing and Market Availability Plans

Currently in Phase II/III clinical development.

Summary

Avacincaptad pegol is in clinical development for the treatment of adults with geographic atrophy secondary to dry age-related macular degeneration (dry AMD). AMD causes gradual, irreversible damage to the centre of the retina of the eye, called the macula, which is needed for seeing visual details. In advanced disease, patches of damage called geographical atrophy (GA) develop on the retina, causing blind spots. It is thought that GA is caused when ageing processes in the retina cause inflammation that starts to cycle out of control, destroying retina cells. GA is irreversible, and it cannot be prevented as ageing is the main risk factor. It is a leading cause of vision loss in the UK. Central vision loss caused by GA increases dependency, vulnerability to falls, and can lead to depression. Currently, there are no recommended treatments for GA in the UK.

Avacincaptad pegol is a biological medicine that was created to interrupt the cycle of inflammation. It is administered directly into the eye, by monthly injections. Avacincaptad pegol binds to one of the key parts of the complement system and stops it from triggering inflammation and cell damage. The target of avacincaptad pegol, called C5 protein, becomes unable to split into two, which is how it signals for more inflammation. In and around the patches of GA the complement system is more active than usual. By damping down the complement system inflammation signals, avacincaptad pegol slows the growth of GA patches on the macula and vision loss is reduced. If licensed, avacincaptad pegol will provide treatment for dry AMD/GA.

Proposed Indication

For the treatment of adults with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).[1]

Technology

Description

Avacincaptad pegol (Zimura, Izervay) is a complement inhibitor.[2] It is a pegylated RNA aptamer engineered to bind and inhibit the C5 component of the complement cascade that leads to the breakdown of retinal cells.[3,4] It may prevent the C5 protein cleaving into C5a and C5b, the key terminal effector components of the complement cascade, signalling for production of the membrane attack complex and leading to cell death.[3-5] Complement activity is found in GA lesions and areas just outside the lesion, and may increase cell damage rates, thereby increasing the risk of lesion growth.[6]

Avacincaptad pegol is currently in phase III clinical development (NCT04435366; NCT05536297) for the treatment of GA that is secondary to AMD. It is administered by monthly intravitreal (IVT) injection of 2mg in each affected eye to slow the progression of retinal damage.[1,5,7]

Key Innovation

Despite GA being considered by patients as debilitating as advanced cancer or stroke, and carrying a high risk of developing clinical depression, there are currently no recommended treatments for GA in the UK.[6,8] Treatment for GA is a significant unmet clinical need that has been increasing in the UK over the last decade.[9,10] Local inhibition of the complement pathway within the eye is a new therapeutic target for slowing GA progession.[6,11] If licensed, avacincaptad pegol will offer a treatment option for people with GA (secondary to AMD) who currently have no therapies available.

Regulatory & Development Status

Avacincaptad pegol does not currently have marketing authorisation in the EU/UK for any indication.

An MAA was submitted to the EMA in July 2023 for the treatment of GA.[12]

Avacincaptad pegol is in phase II clinical development for autosomal recessive Stargardt disease 1 and (in combination with ranibizumab) for neovascular ('wet') AMD.[13]

Avacincaptad pegol has the following regulatory designations/awards:

- Recommended by the US FDA for slowing the progression of lesions of GA in June 2023.[4]
- A Priority Review designation from the US FDA in February 2023.[14]
- A Breakthrough Therapy by the US FDA for GA in November 2022.[15]
- A Fast Track designation from the US FDA for GA in March 2020.[16]

Patient Group

Disease Area and Clinical Need

The macula is the centre of the retina that is responsible for high quality central vision. AMD is a chronic progressive degenerative disease of the macula typically affecting people over the age of 50 years. There are two types of advanced forms of the disease, commonly called dry and wet AMD. Dry AMD is a slowly

deteriorating condition with no treatment at present.[10] In advanced dry AMD, GA can occur, with lesions forming on the macula, which progress from blind spots to irreversible, bilateral central vision loss.[2,6] Once lesions progress to the centre of the macula (called the fovea), central vision and visual acuity function are severely impaired.[6] People with advanced AMD and central vision loss cannot drive, read or recognise faces.[8] The most important risk factors for GA are increasing age and family history, while smoking and genetic mutations in the complement system are additional risk factors.[6]

AMD is the most common cause of visual impairment in the older population significantly affecting their quality of life and independence.[10] In the UK, AMD affects 1 in 200 people at age 60 years, rising to 1 in 5 at age 80 years.[17] The UK prevalence of GA is estimated from a 2012 analysis combined with updated demographics.[10,18] The 2020 estimate was 354,000 cases of GA (over half of all advanced AMD cases) and on a rising trajectory due to the anticipated older population.[9] The estimated incidence per year of new GA cases in 2020 was 51,000.[9] AMD affects men and women equally, but the incidence is higher in women as they typically live longer than men.[17]

Recommended Treatment Options
NICE does not currently recommend any treatments for dry AMD or GA. Self-monitoring is recommended as treatment is required if secondary 'wet'/neovascular AMD develops.[19]

Clinical Trial Information

Trial	**ISEE2008; GATHER2;** NCT04435366; A phase 3 multicenter, randomized, double masked, sham- controlled clinical trial to assess the safety and efficacy of intravitreal administration of zimura (complement C5 inhibitor) in patients with geographic atrophy secondary to age-related macular degeneration **Phase III** – completed **Locations:** 12 EU countries, UK, USA, Canada and other countries. **Study completion date:** August 2023	**ISEE2009**; NCT05536297; 2022-002860-59; An open-label extension (OLE) phase 3 trial to assess the safety of intravitreal administration of avacincaptad pegol (complement C5 inhibitor) in patients with geographic atrophy who previously completed phase 3 study ISEE2008 (GATHER2). **Phase III** – enrolling by invitation **Locations:** 8 EU countries, UK, USA, Canada, Argentina, Colombia, Israel. **Primary completion date:** January 2025
Trial Design	Randomised, parallel assignment, double masked	Open label extension
Population	N=448 (actual); adults 50 years or over with diagnosis of non-foveal GA secondary to dry AMD.	N=400 (estimated); adults over 50 diagnosed with GA who completed study ISEE2008 (Gather2) in either arm of study.
Intervention(s)	Avacincaptad pegol, 2mg intravitreal injection monthly for 11 months. Thereafter to month 23, randomisation to either monthly or every-other-month injections (alternating with sham).	Monthly avacincaptad pegol 2 mg from month 1 to 17 (maximum 17 total doses)
Comparator(s)	Sham administration	-

Outcome(s)	Mean rate of change in GA lesion size over 12 months (measured at baseline, month 6, and month 12).[20]	Adverse effects [time frame: month 18].
Results (efficacy)	From baseline to month 12, the mean rate of square-root-transformed GA area growth was 0.336 mm/year (SE 0.032) with avacincaptad pegol 2 mg and 0.392 mm/year (0.033) with sham, a difference in growth of 0·056 mm/year (95% CI 0.016–0.096; p=0.0064), representing a 14% difference between the avacincaptad pegol 2 mg group and the sham group.[20]	-
Results (safety)	Adverse events in the study eye occurred in 110 (49%) patients in the avacincaptad pegol 2 mg group and 83 (37%) in the sham group. There were no endophthalmitis, intraocular inflammation, or ischaemic optic neuropathy events over 12 months. To month 12, macular neovascularisation in the study eye occurred in 15 (7%) patients in the avacincaptad pegol 2 mg group and nine (4%) in the sham group, with exudative macular neovascularisation occurring in 11 (5%) in the avacincaptad pegol 2 mg group and seven (3%) in the sham group.[20]	-

Clinical Trial Information

Trial	NCT02686658; 2015-003991-56; A phase 2/3 randomized, double-masked, controlled trial to assess the safety and efficacy of intravitreous administration of Zimura™ (anti-C5 aptamer) in subjects with geographic atrophy secondary to dry age-related macular degeneration **Phase 2/3** - completed **Locations** – 5 EU countries, USA and Israel **Study completion date:** April 2020
Trial Design	Randomised parallel assignment, double-masked.
Population	N=286 (actual); age 50 years and over; diagnosis of non-foveal GA secondary to dry AMD.
Intervention(s)	Monthly avacincaptad pegol intravitreal injections at different doses for 18 months: • 1mg (50ul) • 2mg (100ul) • 2mg (100ul) followed by sham administration • 4mg (two consecutive 100ul IVT injections)
Comparator(s)	• Single sham administration, monthly • Two consecutive sham administrations, monthly.

Outcome(s)	Primary outcome: Change from baseline in geographic atrophy. See trial record for full list of other outcomes.
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of avacincaptad pegol is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development: Pegcetacoplan for treating geographic atrophy (TA4041). Expected June 2024.
- NICE guideline. Age-related macular degeneration (NG82). January 2018.

NHS England (Policy/Commissioning) Guidance

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Other Guidance

The Royal College of Ophthalmologists, Commissioning Guidance - Age Related Macular Degeneration Services (2021)[10]

Additional Information

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