Health Technology Briefing
November 2021

Pegcetacoplan for treating geographic atrophy

Company/Developer	Apellis Pharmaceuticals Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 12106	NICE ID: 10585	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Pegcetacoplan is in clinical development for the treatment of geographic atrophy of the macula, secondary to age-related macular degeneration (AMD). AMD is an eye disease that most commonly occurs in people aged over 70 years that affects the middle part of the vision. Some patients with AMD will develop geographic atrophy, which is an advanced form of AMD, where cells located in certain regions of the retina waste away leading to blind spots in the visual field. The disease is progressive and irreversible and as visual function declines, difficulties in reading and mobility can occur. Geographic atrophy results in a significant decline in patient quality of life and accounts for 26% of legal blindness in the UK. There is a significant need in this patient group as currently there are no treatment options available that can stop or reverse progression of the disease.

Pegcetacoplan is a medicinal product that works by attaching to, and blocking, a protein called C3 which is involved in over-activation of a process known as the complement cascade. Over-activation of this process leads to increased inflammation and the development of geographic atrophy. Blocking the C3 protein can regulate the complement cascade and stop progression of geographic atrophy. If licenced, pegcetacoplan would offer a treatment option in for these patients who currently have none available.

Proposed Indication

Adults patients with geographic atrophy secondary to age-related macular degeneration.[4,5]

Technology

Description

Pegcetacoplan (APL-2) is a synthetic cyclic peptide conjugated to a polyethylene glycol (PEG) polymer that binds to the complement protein C3 and its activation fragment C3b, regulating C3b cleavage and the generation of downstream complement activation which is implicated in the pathophysiology of geographic atrophy.[1-3]

In the phase III clinical trials (DERBY, NCT03525600 and OAKS, NCT03525613) patients are given a single dose of pegcetacoplan (15mg/0.1ml), which is administered via intravitreal injection. One cohort receives the injection every month for 24 months and the other receives the injection every other month for 24 months.[4,5]

Key Innovation

There are currently no approved therapies for geographic atrophy creating a large unmet need in this patient group.[2,6] In phase 2 clinical trials, the monthly injection of pegcetacoplan has been demonstrated to reduce geographic atrophy growth rate by 29% compared to sham treatment.[7] In the ongoing Phase 3, in a prespecified combined analyses of the primary endpoint of both Derby and Oaks, Pegcetacoplan reduced lesion growth by 17% (monthly) ($p<0.0001$) vs Sham and 14% (every other month) $p=0.0012$ vs Sham.[8]

Regulatory & Development Status

In October 2021, subcutaneous pegcetacoplan received a positive Committee for Medicinal Products for Human Use (CHMP) opinion for treating adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.[9]

In July 2018, pegcetacoplan was granted a fast track designation by the FDA for the treatment of patients with geographic atrophy.[10]

Pegcetacoplan is also in phase II and/or III development for several other systemic and local indications including:[11]

- Cold agglutinin disease
- Post-transplant recurrence of C3 glomerulopathy or immune complex membranoproliferative glomerulonephritis IC-MPGN
- Amyotrophic lateral sclerosis

Patient Group

Disease Area and Clinical Need

Geographic atrophy is an advanced, vision-threatening form of age-related macular degeneration (AMD). It is a degenerative disease by progressive and irreversible loss of the retinal pigment epithelium (RPE), photoreceptors, and underlying choriocapillaris.[3] Patients with early/intermediate AMD and geographic atrophy experience increased visual impairment under low-light conditions. As the disease progresses large central scotomas (visual blind spots) develop, effectively resulting in legal blindness.[3,12] The loss of visual function associated with geographic atrophy is usually bilateral, with half of patients developing the disease in both eyes within seven years of the initial diagnosis.[3] The level of visual function that an individual with geographic atrophy has is determined by the remaining area that experienced degeneration relative to the fovea. Geographic atrophy causes significant challenges to affected individuals due to difficulties reading, poor distance visual acuity and seeing in low-light conditions which can result in a loss of mobility and independence. Advanced AMD, has been estimated to cause a 63% reduction in patient quality of life.[13] A leading contributor to the development of AMD and geographic atrophy is inappropriate activation of complement-cascade mediated inflammation.[3] Risk factors for developing geographic atrophy include: increasing age (the disease is most common amongst those aged over 70); obesity; heart disease; race (more common among Caucasians); smoking; and having family history of AMD.[14]

The prevalence of geographic atrophy in the UK is between 1.3% for those aged over 50 and 6.7% in those aged over 80 years.[15] In the UK, geographic atrophy accounts for 26% of legal blindness and a retrospective cohort study of patients found that over time, 16% of those who developed the disease became legally blind, (median time to outcome, 6.2 years).[16,17] The same study also found that 66.7% of patients became ineligible to drive (median time to outcome, 1.6 years), and in the worse-seeing eye, 40.1% lost >10 letters in 2.4 years. [17] In England, in 2020-21 there were 52,204 finished consultant episodes (FCEs) and 52,142 admissions for degeneration of macula and posteria pole (ICD-10 H35.3) which resulted in 51,370 day cases and 746 FCE bed days.[18]

Recommended Treatment Options

There are currently no pharmacological therapies approved for the treatment of geographic atrophy, [19]

Clinical Trial Information

Trial	**OAKS**, NCT03525613; A Phase 3, Multi-Center, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of Intravitreal Pegcetacoplan Therapy With Sham Injections in Patients With Geographic Atrophy Secondary to Age-Related Macular Degeneration **Phase III** – active, not recruiting **Locations:** 6 EU, United Kingdom, United States, Canada and other countries. **Primary completion date:** July 2021
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N=600 (planned); adults aged 60 years and older; clinical diagnosis of geographic atrophy of the macula secondary to AMD as determined by the investigator and confirmed by the reading centre

Intervention(s)	Pegcetacoplan (intravitreal injection)
Comparator(s)	Sham procedure
Outcome(s)	Primary outcome measure: • Change from baseline to month 12 in total area of geographic atrophy lesions in the study eye (in mm^2) based on fundus autofluorescence (FAF) [Time Frame: 12 months] See trial record for full list of outcome measures
Results (efficacy)	This study met the primary endpoint for both monthly and every-other-month treatment with pegcetacoplan, demonstrating a significant reduction in GA lesion growth of 22% (p=0.0003) and 16% (p=0.0052), respectively, compared to pooled sham at 12 months. [8]
Results (safety)	Pegcetacoplan was well tolerated and had a favourable safety profile. When combining the safety results of this study and the other phase III DERBY study, the pooled rate of new-onset exudations was 6.0% of patients in the monthly pegcetacoplan groups, 4.1% in the every-other-month pegcetacoplan groups, and 2.4% in the sham groups. Two cases of confirmed infectious endophthalmitis and one case of suspected infectious endophthalmitis were observed in the study eye out of a total of 6,331 injections (0.047%). Thirteen events of intraocular inflammation were observed in the studies (0.21% per injection). No events of retinal vasculitis or retinal vein occlusion were observed. There were no clinically relevant changes in vision for patients who developed infectious endophthalmitis or intraocular inflammation.[8]

Clinical Trial Information	
Trial	**DERBY**, NCT03525600; A Phase 3, Multi-Center, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of Intravitreal Pegcetacoplan Therapy With Sham Injections in Patients With Geographic Atrophy Secondary to Age-Related Macular Degeneration **Phase III** – Active, not recruiting **Locations:** 6 EU, United Kingdom, United States, Canada and other countries **Primary completion date:** July 2021
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N=600 (planned); adults aged 60 years and older; clinical diagnosis of geographic atrophy of the macula secondary to AMD as determined by the investigator and confirmed by the reading centre
Intervention(s)	Pegcetacoplan (intravitreal injection)
Comparator(s)	Sham procedure
Outcome(s)	Primary outcome measure: • Change from baseline to month 12 in total area of geographic atrophy lesions in the study eye (in mm^2) based on FAF [Time Frame: 12 months]

	See trial record for full list of outcome measures
Results (efficacy)	This study did not meet the primary endpoint of geographic atrophy lesion growth, showing a reduction of 12% (p=0.0528) and 11% (p=0.0750) with monthly and every-other-month treatment, respectively, compared to pooled sham at 12 months. [8]
Results (safety)	Pegcetacoplan was well tolerated and had a favourable safety profile. When combining the safety results of this study and the other phase III OAKS study, the pooled rate of new-onset exudations was 6.0% of patients in the monthly pegcetacoplan groups, 4.1% in the every-other-month pegcetacoplan groups, and 2.4% in the sham groups. Two cases of confirmed infectious endophthalmitis and one case of suspected infectious endophthalmitis were observed in the study eye out of a total of 6,331 injections (0.047%). Thirteen events of intraocular inflammation were observed in the studies (0.21% per injection). No events of retinal vasculitis or retinal vein occlusion were observed. There were no clinically relevant changes in vision for patients who developed infectious endophthalmitis or intraocular inflammation.[8]

Clinical Trial Information	
Trial	**FILLY**, NCT02503332; A Phase II, Multicentre, Randomized, Single-Masked, Sham-Controlled Study of Safety, Tolerability and Evidence of Activity of Intravitreal APL-2 Therapy in Patients With Geographic Atrophy **Phase II** – completed **Locations:** United States, Australia and New Zealand **Actual study completion date:** January 2018
Trial Design	Randomised, single group assignment, single masking (participant)
Population	N=246; adults aged 50 years and older; diagnosis of geographic atrophy secondary to age-related macular degeneration
Intervention(s)	Pegcetacoplan (intravitreal injection)
Comparator(s)	Sham procedure
Outcome(s)	Primary outcome measures: • Least square mean change from baseline (at screening) in square root of geographic atrophy lesion size in the study eye [Time Frame: baseline to month 12] • Number of subjects with treatment emergent adverse events (TEAEs), including by severity [Time Frame: From the time of first study drug administration (day 1) up to month 12 (data cut-off data)]
Results (efficacy)	Pegcetacoplan met its primary endpoint of reducing the growth rate of the geographic atrophy lesion compared to sham after 12 months of treatment. Pegcetacoplan administered monthly via intravitreal injection showed a 29% (p=0.008) reduction in the rate of geographic atrophy lesion growth compared

	to sham after 12 months of treatment. With every other month administration of APL-2, a 20% (p=0.067) reduction was observed.[20]
Results (safety)	No changes in the safety profile were observed in the 12-18 month period. Over the full 18-month study period, a total of 26 cases of exudative AMD were reported by the investigators. These were seen more frequently in the APL-2-treated patients (18 in the monthly treatment group, 7 in the every other month treatment group and 1 in the sham control group). No negative impact on visual acuity was observed.[20]

Estimated Cost

The estimated cost of pegcetacoplan is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Age-related macular degeneration (NG82). January 2018.

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. Age related macular degeneration: guidelines for management. 2013.[21]

Additional Information

Apellis pharmaceuticals 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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