5.08 PEGECETACOPLAN, Solution for intravitreal injection 15 mg in 0.1 mL (150 mg per mL), Syfovre®, APELLIS AUSTRALIA PTY LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a General Schedule Authority Required listing for pegcetacoplan for the treatment of non-subfoveal geographic atrophy (GA) that is secondary to age-related macular degeneration (AMD).

1.2 Listing was requested on the basis of a cost-utility analysis (CUA) versus best supportive care (BSC). The key components of the submission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with bilateral GA secondary to AMD, with an intact fovea (non-subfoveal lesion i.e., ≥1 µm from the foveal centre) and central vision threatened by GA lesion growth (GA lesion is ≤750 µm from the foveal centre) OR the GA lesions that are located beyond the 750 µm radius from the foveal centre, and where historical imaging indicates lesion progression is toward the foveal centre, and is located within the macula (defined as the 5.5 mm diameter area), and the fellow eye has a subfoveal GA lesion (i.e., a compromised fovea, where the GA lesion involves the foveal centre point)
Intervention	Pegcetacoplan administered at a dose of 0.1 mL of 150 mg/mL (15 mg) as an intravitreal injection every other month (in the better seeing eye)
Comparator	Best supportive care
Outcomes	Primary endpoint: Change in the total area of GA lesions in the study eye at 12 months as measured by FAF from baseline compared to sham Key secondary endpoints: Change in the total area of GA lesions in the study eye at 24 months as measured by FAF from baseline compared to sham Monocular maximum reading speed (study eye) at 24 months, as assessed by the MNREAD or Radner Reading Charts FRI Index score at 24 months (subject-level assessment) NL-BCVA at 24 months score in the study eye Change from baseline in the mean threshold sensitivity of all points measured by mesopic microperimetry (in patients in the OAKS study) Change in the number of scotoma points in the study eye at 24 months measured by mesopic microperimetry (in patients in the OAKS study) Conversion of central 4 or 16 points to scotomata at 24 months measured by mesopic microperimetry (in patients in the OAKS study) Long-term safety and efficacy of pegcetacoplan at month 48 assessed in GALE study
Clinical claim	Pegcetacoplan significantly slows GA lesion growth and is superior, compared to best supportive care, and has an acceptable safety profile

Source: Table 1, p37 of the submission.
AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; FAF = fundus autofluorescence; FRI = Functional Reading Independence; GA = geographic atrophy; mm = millimetre; MNREAD = Minnesota Low Vision Reading Test; NEI VFQ = National Eye Institute Visual Function Questionnaire; NL-BCVA = normal-luminance best-corrected visual acuity

2 Background

Registration status

2.1 Pegcetacoplan administered as an intravitreal injection received Therapeutic Goods Administration (TGA) registration on 29 January 2025 for the treatment of adult patients with GA secondary to AMD with an intact fovea and when central vision is threatened by GA lesion growth.

2.2 Pegcetacoplan administered as a 1,080 mg subcutaneous infusion is currently TGA approved, and PBS listed for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria who have an inadequate response or are intolerant of a C5 inhibitor.

Previous PBAC consideration

2.3 This is the second PBAC submission for pegcetacoplan for the treatment of GA. The first submission was lodged for consideration at the March 2024 PBAC meeting but was subsequently withdrawn prior to consideration by ESC or the PBAC due to a delay in regulatory approval by the TGA. Pegcetacoplan as a subcutaneous infusion is listed on the PBS for the treatment of paroxysmal nocturnal haemoglobinuria.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Pegcetacoplan					
Pegcetacoplan, 15 mg/0.1 mL injection, 0.1 mL vial	$[redacted] published price $[redacted] effective price	1	1	2	Syfovre
Category / Program: General Schedule					
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐					
Restriction type: ☒Authority Required (telephone/online PBS Authorities system) ☒Authority Required (in writing only via post/HPOS upload)					
Condition: Geographic Atrophy secondary to age-related macular degeneration					
Indication: Geographic Atrophy secondary to age-related macular degeneration					
Treatment Phase: Initial					
Clinical criteria:					
Patient must have geographic atrophy (GA) secondary to age-related macular degeneration (AMD)					
AND					
The condition must be diagnosed by optical coherence tomography; OR The condition must be diagnosed by fundus autofluorescence					
AND					
The treated eye has an intact fovea, i.e. non-subfoveal lesions (defined as lesions ≥1 µm from the foveal centre point)					
AND					
The treated eye has central vision threatened by GA lesion growth (defined as GA lesions that are either located within a 750 µm radius from the foveal centre; OR the GA lesions that are located beyond the 750 µm radius from the foveal centre, and where historical imaging indicates lesion progression is toward the foveal centre, and is located within the macula (defined as the 5.5 mm diameter area)					
AND					
The other non-treated eye has vision impairment defined as the fovea no longer being intact (subfoveal GA, i.e. a compromised fovea, where the GA lesion involves the foveal centre point)					
AND					
The treatment must be as monotherapy					
AND					
The treatment must be the sole PBS-subsidised therapy for this condition.					
Treatment criteria:					
Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist.					

Prescribing Instructions: administer dose of 15 mg (0.1 mL of 150 mg/mL solution) administered as an intravitreal injection
Administrative Advice: Authority approval for initial treatment must be sought. The first authority application for each eye must be made via the Online PBS Authorities System (real time assessment) or by calling Services Australia. When applying by phone, the prescriber must provide: (1) Details (date, unique identifying number/code or provider number) of the optical coherence tomography or fundus autofluorescence report. If the application is submitted through HPOS form upload or mail, it must include: (a) A completed authority prescription form; and (b) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). All reports must be documented in the patient's medical records. Note No increase in the maximum number of repeats may be authorised. Note No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye.

Category / Program: General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required - Streamlined
Condition: Geographic Atrophy secondary to age-related macular degeneration
Indication: Geographic Atrophy secondary to age-related macular degeneration
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye
AND
Patient must have geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
AND
The treatment must be as monotherapy
AND
The treatment must be the sole PBS-subsidised therapy for this condition.
AND
The treated eye has an intact fovea, i.e. non-subfoveal lesions (defined as lesions ≥1 µm from the foveal centre point)
AND
The treated eye has central vision threatened by GA lesion growth (defined as GA lesions that are either located within a 750 µm radius from the foveal centre); OR the GA lesions that are located beyond the 750 µm radius from the foveal centre, and where historical imaging indicates lesion progression is toward the foveal centre, and is located within the macula (defined as the 5.5 mm diameter area)
AND
The other non-treated eye has vision impairment defined as the fovea no longer being intact (subfoveal GA, i.e. a compromised fovea, where the GA lesion involves the foveal centre point)
Treatment criteria:
Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist
Prescribing Instructions: Administer dose of 15 mg (0.1 mL of 150 mg/mL solution) administered as an intravitreal injection.

For continued treatment the patient must demonstrate treatment benefit from this drug and meet the initial criteria for treatment eligibility, meeting the definition for an intact fovea (defined as non-subfoveal lesions ≥1 µm from the foveal centre point) in the treated eye with central vision threatened by GA lesion growth (defined as GA lesions that are either located within a 750 µm radius from the foveal centre); OR the GA lesions that are located beyond the 750 µm radius from the foveal centre, and where historical imaging indicates lesion progression is toward the foveal centre, and is located within the macula [defined as the 5.5 mm diameter area]).
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Note Special Pricing Arrangements apply. Note No increase in the maximum quantity or number of units may be authorised for applications for treatment of one eye.

3.1 The submission stated that the initial treatment and continuing eligibility criteria for the proposed pegcetacoplan PBS listings are aligned with the patient population from the pivotal trials. In the pivotal trials, DERBY and OAKS, approximately two-thirds of participants had a subfoveal lesion at baseline, inconsistent with the requested clinical criteria for the PBS listing of pegcetacoplan, which was patients with a non-subfoveal lesion. However, the submission did present a subgroup analysis of patients in DERBY and OAKS with lesions which were ≥1 µm from the fovea (non-subfoveal) or <1 µm from the fovea (subfoveal). This aligned with the proposed PBS restriction for treatment of the eye with non-subfoveal lesions.

3.2 The TGA listing states that patients must have an intact fovea but does not provide a description of this, whereas the proposed PBS listing defines it as lesions ≥1 µm from the foveal centre point. The ESC considered the definition in the PBS listing was clinically appropriate.

3.3 The requirement for patients to have a compromised fovea in the non-treated eye is not consistent with the TGA indication or key trials which enrolled patients with both bilateral-GA (treated the worse eye) and with only one eye impacted by GA. This change was suggested by the Advisory Committee on Medicines (ACM) which noted that "an ideal patient for this treatment would be one that had already lost vision in one eye and be motivated to accept higher risks and less certainty in outcomes in order to potentially prevent or delay the same outcome for their other eye." The ESC considered this was a reasonable inclusion in the listing. Overall, the ESC considered the criteria of the initial and continuing treatment restrictions were clinically sound.

3.4 The submission included a request for a grandfathering clause to provide [redacted]. The evaluation considered it was unclear how many patients the grandfather clause will apply to. The grandfathering restriction aligns with the proposed PBS initiation restriction which is narrower than the population enrolled in the key trials. If the purpose of the grandfathering listing is to provide [redacted], then the proposed wording would exclude trial patients who have an intact fovea in the non-treated eye. The pre-PBAC response clarified that [redacted]. A proportion of the patients [redacted]

[redacted] were anticipated to meet the proposed PBS restriction and were captured in the estimated usage and financial impacts.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 GA represents the advanced, non-neovascular (or "dry") form of AMD, a leading cause of irreversible vision loss in older adults[1]. AMD is a progressive degenerative disease affecting the central retina (macula), resulting in central visual impairment[2]. GA is characterised by well-demarcated areas of retinal atrophy involving the retinal pigment epithelium (RPE), photoreceptors, and underlying choriocapillaris. This condition typically develops slowly but results in permanent visual disability[1]. The burden of GA is increasing in ageing populations, including in Australia, where it poses a growing public health concern.

4.2 The macula is the central portion of the retina, approximately 5.5 mm in diameter, responsible for high-acuity central vision[3]. At the centre lies the fovea, which is densely populated with cone photoreceptors and critical for tasks requiring fine visual detail, such as reading and facial recognition[3]. GA is defined by discrete areas of RPE and photoreceptor cell loss with associated retinal thinning and hypopigmentation. Lesions typically originate in the perifoveal region and gradually expand centripetally to involve the fovea[4]. The progression rate is variable, but once foveal involvement occurs, central visual acuity is markedly impaired. The complement cascade, particularly the alternative pathway involving components such as C3 and C5, has been implicated in lesion expansion and RPE degeneration[5].

4.3 The submission states that 75% of advanced AMD in Australia is GA and that this is the equivalent of approximately 86,000 people. The prevalence increases substantially with age; individuals over 85 years have a markedly higher risk, with one in five affected by GA in at least one eye.

4.4 Risk factors associated with GA include advanced age, genetic predisposition, smoking, and a family history of AMD. The condition is equally distributed between sexes, although some studies suggest a slightly higher incidence in females[5].

4.5 The submission stated that in Australia there are no specific guidelines for the treatment of GA. There are currently no other drugs listed on the PBS for this population. As such, the proposed clinical management algorithm has pegcetacoplan,

[1] Ieckenstein M, Mitchell P, Freund KB, Sadda S, Holz FG, Brittain C, et al. 2018. The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. *Ophthalmology*. 125(3):369-90.

[2] Flores R, Carneiro Â, Vieira M, Tenreiro S, Seabra MC.2021. Age-Related Macular Degeneration: Pathophysiology, Management, and Future Perspectives. *Ophthalmologica*. 244(6):495-511

[3] Rehman I MN, Motlagh M, et al. 2023. Anatomy, Head and Neck, Eye Fovea. https://www.ncbi.nlm.nih.gov/books/NBK482301/: Treasure Island (FL): StatPearls Publishing.

[4] Mulfaul K, Russell JF, Voigt AP, Stone EM, Tucker BA, Mullins RF. 2022. The Essential Role of the Choriocapillaris in Vision: Novel Insights from Imaging and Molecular Biology. *Annu Rev Vis Sci*. 15;8:33-52.

[5] Bakri SJ, Bektas M, Sharp D, Luo R, Sarda SP, Khan S. 2023. Geographic atrophy: Mechanism of disease, pathophysiology, and role of the complement system. *J Manag Care Spec Pharm*. 29(5-a Suppl):S2-s11.

in combination with BSC, placed as the only treatment for GA. The proposed clinical management algorithm did not specify the exact population defined in the PBS listing, which consists of patients with non-subfoveal lesions who have impaired vision in the non-treated eye.

4.6 Pegcetacoplan is a complement inhibitor that inhibits activation of the complement protein C3. The complement cascade is a part of the immune system made up of circulating inactive proteins which are cleaved into active pro-inflammatory cytokines, which enhance immune activity. Pegcetacoplan is an asymmetrical molecule composed of two identical pentadecapeptides covalently bound to the ends of a linear polyethylene molecule[6].

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated BSC as the main comparator. BSC was defined as supportive therapies including dietary modifications, cessation of smoking, low vision support and rehabilitation. The main argument provided in support of this nomination was that there are no therapies for GA approved by the TGA, at the time of the submission, or listed on the PBS. The ESC agreed with the evaluation that the nominated comparator was appropriate.

5.2 The submission also nominated avacincaptad pegol as a near market comparator, stating that it is approved by the United States Food and Drug Administration (FDA) and is currently undergoing evaluation by the TGA for the treatment of GA secondary to AMD. This was appropriate. No clinical comparison with avacincaptad pegol was presented.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician described the severity of the condition and the impact of losing central vision on patients' quality of life, the risk of falls and the loss of independence. The clinician addressed the lack of significant benefit in functional outcomes, such as BCVA, from the key trial evidence. The clinician noted that approximately two thirds of patients in the clinical trial had subfoveal lesions in the treated eye, and as such the inclusion of both subfoveal and non-subfoveal lesions likely introduced variability and diluted the treatment effect. The clinician presented microperimetry data from the key trial and explained the relevance of this outcome at detecting functional vision loss, as it reports on the

[6] Nadeem A, Malik IA, Shariq F, Afridi EK, Taha M, Raufi N, et al. (2023) Advancements in the treatment of geographic atrophy: focus on pegcetacoplan in age-related macular degeneration. *Ann Med Surg (Lond)*. 85(12):6067-77.

number of spots (perception of light) lost and where they were located in the central area. The significant difference in the risk of reducing the centre 16 points was expected to be meaningful. The clinician responded to PBAC enquiries on the incidence of adverse events and confirmed that patients with "dry" AMD have an increased risk of developing neovascular AMD, and those patients would be treated with VEGF inhibitors to control neovascular AMD before continuing with treatment for dry AMD. The clinician explained that intraocular inflammation was an issue with all intravitreal treatments and clinicians are aware of these issues and careful with treating patients with a history of adverse reactions. The PBAC considered that the hearing was informative as the clinical perspective on treating this disease aligned with the key issues for PBAC consideration.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (6), health -care related organisations (3), consumer groups (1) and individuals (69) via the Office of Health Technology Assessment Consultation Hub. The PBAC acknowledged the lived experience of individual consumers using pegcetacoplan under private prescription, and the benefits associated with slowing progression of GA and preservation of existing eyesight, as these outcomes most directly contributed to maintenance of quality of life and independence. The PBAC noted the financial pressures associated with private prescription access to pegcetacoplan, with consumers potentially having to choose preservation of eyesight in only one eye due to cost, as well as accessibility to health practitioners who charged varying fees for administration of pegcetacoplan. It was also noted that some using the medicine said that prior to commencing treatment in their better eye a dose was administered to the inferior eye to test for adverse reactions. The PBAC noted that the proposed PBS subsidisation would limit access to treatment of only one eye for the highest priority patients, who have already experienced visual impairment in the other eye.

6.3 The PBAC noted feedback from prospective consumers who would like to access the medicine to treat their own health condition which described the significant cost barriers associated with access to pegcetacoplan especially for those at advanced age. The input described the impact that slowing progression of GA would have on different aspects of quality of life, including independent living, physical mobility and mental health. Similar feedback was received from Australian Eye Specialists collated on behalf of consumers unable to prepare individual written submissions.

6.4 The PBAC also noted advice from carers regarding the benefit of treatments that slowed progression of GA in supporting maintenance of quality of life. The input described how such treatment would limit the costs associated with carers providing direct assistance for everyday activities and the secondary costs associated with the procurement of other visual aids and services to mitigate the limitations associated with progressive loss of vision.

6.5 The PBAC acknowledged the input from health care professionals currently managing

or diagnosing patients with GA and advanced AMD. Input from ophthalmologists currently prescribing and administering pegcetacoplan noted the stabilisation of visual acuity in individual consumers. The input also acknowledged some of the observed side effects associated with treatment (including inflammation, injection site irritation and sight threatening vasculitis) and the limited long-term efficacy and safety data at this stage of pegcetacoplan use in clinical care.

6.6 The PBAC noted the advice received from Sight For All, Macular Disease Foundation Australia (MDFA) and OKKO Eye Specialist Centre regarding the limitations of current treatment options (e.g. oral vitamin supplements to support retinal health) to slow the progression of vision loss, as well as the quality of life benefits that use of pegcetacoplan may provide with delayed progression of GA. Input from MDFA noted the impact of vision loss on the number of falls and fractures and evidence that it could result in earlier entry into Residential Aged Care. MDFA input acknowledged the lack of visual acuity improvement associated with use of pegcetacoplan in the intended target population which could affect patient adherence with treatment. The input also advised limiting PBS patient eligibility initially to those with bilateral GA secondary to AMD to reduce potential complications associated with the use of pegcetacoplan and to support documentation of treatment related adverse events as part of evaluating long-term safety and efficacy.

Clinical trials

6.7 The submission was based on 2 phase 3 randomised controlled trials (RCTs) comparing pegcetacoplan intravitreal (IVT) monthly (PM) or every other month (PEOM) to sham injection monthly or every other month: DERBY (n=621) and OAKS (n=637). These were supplemented by two other studies: FILLY (n=246), a phase 2 RCT comparing PM or PEOM with sham injections and GALE (n=780), an ongoing, open label, -long-term extension study to DERBY and OAKS. The submission stated that the final results from GALE are expected in November 2025.

6.8 As the populations enrolled in DERBY and OAKS do not align with the proposed PBS population, the submission presented a post-hoc analysis of patients with non-subfoveal lesions (defined as GA lesions ≥1 µm from the fovea). The included subgroup analysis matched the lesion location criteria in the PBS restriction. However, an analysis was not carried out adjusting for the requirement that patients already have compromised vision in their non-treatment eye. It is uncertain how many patients in the trial would meet this requirement and so such an analysis may not have been possible or informative.

6.9 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
DERBY NCT03525600	APL2-303 Month 24 Clinical Study Report: A phase 3, multicenter, 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 (DERBY).	October 2022

Trial ID	Protocol title/ Publication title	Publication citation
	Heier, J.S., et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials.	*The Lancet* 2023; 402(10411): 1434 – 1448.
OAKS NCT03525613	APL2-304 Month 24 Clinical Study Report: A phase 3, multicenter, 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 (OAKS). Heier, J.S., et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials.	October 2022 *The Lancet* 2023; 402(10411): 1434 – 1448.
FILLY (NCT02503332)	Wykoff, C. C., et al. (2021). "Characterising New Onset Exudation in the Randomised phase 2 FILLY Trial of Complement Inhibitor Pegcetacoplan for Geographic Atrophy." Pfau, M., et al. Association of complement C3 inhibitor pegcetacoplan with reduced photoreceptor degeneration beyond areas of geographic atrophy. Steinle, N. C., et al. Impact of Baseline Characteristics on Geographic Atrophy Progression in the FILLY Trial Evaluating the Complement C3 Inhibitor Pegcetacoplan. Riedl, S., et al. The Effect of Pegcetacoplan Treatment on Photoreceptor Maintenance in Geographic Atrophy Monitored by Artificial Intelligence-Based OCT Analysis. Fu, D. J., et al. Deep-learning automated quantification of longitudinal OCT scans demonstrates reduced RPE loss rate, preservation of intact macular area and predictive value of isolated photoreceptor degeneration in geographic atrophy patients receiving C3 inhibition treatment. Nittala, M. G., et al. Association of Pegcetacoplan With Progression of Incomplete Retinal Pigment Epithelium and Outer Retinal Atrophy in Age-Related Macular Degeneration: a Post-Hoc Analysis of the FILLY Randomised Clinical Trial. Vogl, W. D., et al. Predicting Topographic Disease Progression and Treatment Response of Pegcetacoplan in Geographic Atrophy Quantified by Deep Learning. Liao, D. S., et al. Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomised phase 2 Trial. Mai, J., et al. Comparison of Fundus Autofluorescence Versus Optical Coherence Tomography-based Evaluation of the Therapeutic Response to Pegcetacoplan in Geographic Atrophy.	*Ophthalmology* 2021; 128(9):1325-1336. *Scientific Reports* 2022; 12(1): 17870. *American Journal of Ophthalmology* 2021; 227: 116-124. *Ophthalmology Retina* 2022; 6(11): 1009-1018. *The British Journal of Ophthalmology* 2023; 24: bjo-2022-322672. *JAMA Ophthalmology* 2022; 140(3): 243-249. *Ophthalmology Retina* 2023; 7(1): 4-13. *Ophthalmology* 2020; 127(2): 186-195. *American Journal of Ophthalmology* 2022; 244: 175-182.
GALE NCT04770545	Steinle N., et al. Long-Term Efficacy of Pegcetacoplan in Patients With Geographic Atrophy. Ursula Schmidt-Erfurth, J. M., et al. Effect of Pegcetacoplan on Photoreceptor and Retinal Pigment Epithelium Integrity in Geographic Atrophy in the Phase 3 Trials and GALE Extension Study.	American Society of Retina Specialists 41st Annual Meeting, Seattle WA, 2023. American Society of Retina Specialists 41st Annual Meeting, Seattle WA, 2023.

Source: Table 11, pp71-72 of the submission.

6.10 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Pegcetacoplan (monthly or every other month) vs. sham injection (monthly or every other month)						
Key trials						
DERBY	597	R, DB 24 mths	Low	GA secondary to AMD	Primary: CFB to month 12 in total area of GA lesions Secondary: CFB to month 24 in total area of GA lesions, monocular maximum reading speed, mean FRI Index score, mean NL-BCVA and LL-BCVA scores, mean NEI VFQ-25 distance activity subscale score	Not used
OAKS	614	R, DB 24 mths	Low	GA secondary to AMD	Primary: CFB to month 12 in total area of GA lesions Secondary: CFB to month 24 in total area of GA lesions, monocular maximum reading speed, mean FRI Index score, mean NL-BCVA and LL-BCVA scores, mean NEI VFQ-25 distance activity subscale score, mean threshold sensitivity of all points (study eye) assessed by mesopic microperimetry	Microperimetry
Supportive trials						
FILLY	75	R, DB 18 mths	Low	GA secondary to AMD	Primary: CFB to month 12 in total area of GA lesions Secondary: CFB to month 18 in NL-BCVA and LL-BCVA scores	Not used
GALE	790	OL 36 months	Low	GA secondary to AMD	Primary: Long-term safety of IVT injected pegcetacoplan Secondary: CFB to months 12, 24 and 36 in total area of GA lesion(s), NL-BCVA and LL-BCVA scores, LLD, monocular maximum reading speed and monocular critical print size, binocular maximum reading speed and binocular critical print size, the number of absolute scotomatous points and macular sensitivity assessed by mesopic	Not used

Source: Figure 14 and Figure 15, p75, Table 13, pp76-78, Table 19, p88, and Table 20, p89 of the submission.
AMD = age-related macular degeneration; CFB = change from baseline; DB = double-blind; FRI, Functional Reading Independence Index; GA = geographic atrophy; IVT = intravitreal; LL-BCVA = low-luminance best-corrected visual acuity; LLD = low-luminance deficit; NEI VFQ = National Eye Institute Visual Function Questionnaire; NL-BCVA = normal-luminance best-corrected visual acuity; OL = open label; R = randomised.

Comparative effectiveness

6.11 The key outcomes presented in the submission for the whole trial populations in DERBY and OAKS are presented in Table 4.

Table 4: Results of key primary and secondary outcomes, DERBY and OAKS, MMRM, whole trial populations (mITT)

Trial ID	Treatment arm	Sample size (n)	LS mean (SE)	Difference in LS mean (95% CI) vs sham pooled	% Difference in LS mean vs sham pooled
Primary outcome: Change from baseline in total area of GA lesion(s) (mm^2) (FAF) at month 12					
DERBY	PM	200	1.73 (0.08)	-0.23 (-0.47, 0.01)	-11.7%
	PEOM	199	1.76 (0.07)	-0.21 (-0.44, 0.03)	-10.6%
	Sham (pooled)	193	1.96 (0.10)	NA	NA
OAKS	PM	202	**1.56 (0.08)**	**-0.41 (-0.64, -0.18)**	-20.9%
	PEOM	204	**1.65 (0.08)**	**-0.32 (-0.54, -0.09)**	-16.1%
	Sham (pooled)	205	1.97 (0.08)	NA	NA
Secondary outcomes: Change from baseline in total area of GA lesion(s) (mm^2) (FAF) at month 24					
DERBY	PM	200	**3.23 (0.12)**	**-0.75 (-1.15, -0.34)**	-18.8%
	PEOM	200	**3.34 (0.13)**	**-0.63 (-1.05, -0.22)**	-15.9%
	Sham (pooled)	194	3.97 (0.17)	NA	NA
OAKS	PM	202	**3.12 (0.14)**	**-0.90 (-1.30, -0.50)**	-22.4%
	PEOM	204	**3.28 (0.13)**	**-0.74 (-1.13, -0.36)**	-18.4%
	Sham (pooled)	206	4.03 (0.15)	NA	NA
Change from baseline in NL-BCVA score (ETDRS letters) at month 24					
DERBY	PM	201	-8.13 (1.02)	-1.91 (-4.70, 0.83)	NR
	PEOM	201	-8.95 (1.03)	-2.73 (-5.57, 0.11)	NR
	Sham (pooled)	195	-6.22 (1.02)	NA	NA
OAKS	PM	202	-7.48 (1.05)	0.18 (-2.72, 3.09)	NR
	PEOM	205	-8.53 (1.05)	-0.87 (-3.79, 2.06)	NR
	Sham (pooled)	207	-7.66 (1.07)	NA	NA
Change from baseline in NEI VFQ-25 distance activity subscale score at month 24					
DERBY	PM	188	-8.41 (1.86)	-1.88 (-6.83, 3.07)	NR
	PEOM	188	-6.64 (1.82)	-0.11 (-4.92, 4.70)	NR
	Sham (pooled)	182	-6.53 (1.91)	NA	NA
OAKS	PM	187	-7.98 (1.68)	-0.22 (-4.55, 4.12)	NR
	PEOM	192	-7.81 (1.50)	-0.04 (-4.18, 4.11)	NR
	Sham (pooled)	194	-7.77 (1.68)	NA	NA

Source: Table 37, p117, Table 45, p126, Table 51, p135, and Table 58, p141 of the submission.
CI = confidence interval; EDTRS = Early Treatment Diabetic Retinopathy Study; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least square; mITT = modified intention to treat population; MMRM = mixed-effect model for repeated measures; n = number of participants with event; N = total participants in group; NA = not applicable; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; NL-BCVA = normal-luminance best-corrected visual acuity; NR = not reported; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly;
Bold indicates statistically significant results.

6.12 The DERBY and OAKS trials dosed pegcetacoplan both monthly and every other month. However, the approved product information only includes pegcetacoplan dosed once every other month (approximately every 60 days). As such, it is the PEOM results that are most relevant to the proposed PBS population.

6.13 All efficacy outcomes in the trials were analysed using the modified intention-to-treat (mITT) population, which consisted of all participants assigned to treatment who

received at least one injection of pegcetacoplan or sham and had at least one post-baseline value of GA lesion area in the study eye as assessed by fundus autofluorescence (FAF).

6.14 For the primary outcome of change from baseline (CFB) in total area of GA lesion size at 12 months, statistical significance was achieved in the OAKS trial, which showed a difference in least squares (LS) mean -0.41 (95% confidence interval[CI]: -0.64, -0.18) in the PM arm, and a difference in LS mean of -0.32 (95% CI: -0.54, -0.09) in the PEOM arm, corresponding to a difference of -20.9% and -16.1% in the PM and PEOM groups respectively, compared to sham (pooled). The DERBY trial did not demonstrate a statistically significant difference for the primary outcome in either the PM or PEOM groups.

6.15 The submission stated that there were several imbalances across the treatment groups and carried out a post-hoc covariate adjusted analysis to account for these. The identified imbalances in the DERBY trials were more subjects in the pegcetacoplan treatment groups than in the sham pooled group had multifocal lesions and ≤20 intermediate/large drusen. In the OAKS trial more subjects in the pegcetacoplan treatment groups had non-subfoveal lesions at baseline than in the sham pooled group. When adjusted for these baseline characteristics, an increase was shown in the estimated treatment effect for the PM groups vs sham pooled from −10.6% to −14.4% in DERBY, and from −16.1% to −17.1% in OAKS when compared with the main MMRM analysis without any adjustments. Importantly, these adjustments resulted in the DERBY trials reporting a statistically significant difference between PM and sham (-0.31, 95% CI: -0.54, -0.087) and also between PEOM and sham (-0.29, 95% CI: -0.51, -0.07), while the unadjusted results were not statistically significant.

6.16 The Pre-Sub-Committee Response (PSCR) noted that data from the GALE extension study of DERBY and OAKs reported a percentage difference of -12.7% (difference in LS mean of -0.89 [-1.48 to -0.31]) in GA lesion size for the PEOM to PEOM group (n=267) at integrated month 48. The ESC agreed with the PSCR that these results were consistent with a continued treatment effect on GA lesions out to 48 months.

6.17 Neither the DERBY nor OAKS trials demonstrated statistically significant changes in the visual function outcomes of normal luminance best corrected visual acuity (NL-BCVA), monocular maximum reading speed, functional reading independence (FRI) score, or results on the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25). The ESC considered that, while pegcetacoplan may slow the progression of GA lesion growth, it is uncertain how this will translate into a delay in loss of usable vision required for independent activities of daily living.

6.18 It was also noted during the evaluation that the whole trials populations of the DERBY and OAKS trials do not align with the requested PBS populations as the whole trial populations included patients with subfoveal and non-subfoveal GA lesions at base line. As there are differences in the rate of lesion growth in subfoveal and non-subfoveal lesions, the overall trial results may not be applicable to the proposed PBS population.

6.19 The OAKS trial used microperimetry to map and track areas of retinal sensitivity, with areas of the retina affected by GA lesions having reduced sensitivity to light. Using this, the submission analysed the number of patients who had their central 4 or central 16 microperimetry points, which corresponded to the fovea, converted to scotoma over the course of 24 months.

6.20 Microperimetry is a psychophysical visual function test used to spatially map retinal sensitivity or the level of response of the retina to light stimuli. During a microperimetry test, light stimuli of various intensities are altered to determine the lowest level at which the participant can detect the light. Stimulus intensity is measured in decibels (dB), where a higher score indicates detection of a dimmer stimulus and thus higher retinal sensitivity; a score of 0 dB signifies an absolute scotoma, reflecting a failure to detect the brightest stimulus available on the instrument.

Table 5: Analysis of conversion of all 4 or all 16 central microperimetry points to scotoma in the study eye in OAKS from baseline through to month 24. (mITT)

OAKS	PEOM	Sham	Hazard ratio (95% CI) P value
Conversion of all 4 central points	59/152 (38.8%)	64/146 (43.8%)	**0.64 (0.44, 0.92)**
Conversion of all 16 central points	28/184 (15.2%)	39/181 (21.5%)	**0.52 (0.32, 0.85)**

Source: Table 61, p143 and Table 62, p145 of the submission
CI = confidence interval GA = geographic atrophy; mITT = modified intention-to-treat; PEOM = pegcetacoplan every other month.
Note: Subjects censored on day 1 due to no postbaseline assessment or not at risk for the event were excluded from analysis. The first observed postbaseline assessment with 4 central scotomatous points of 16 central scotomatous points was counted as the event. Model included treatment + baseline GA lesion area (<7.5 mm2 or ≥7.5 mm2) + baseline number of central 16 scotomatous points (categorical)
Bold = statistically significant.

6.21 Based on this analysis, the submission stated that treatment with pegcetacoplan every other month resulted in a statistically significant hazard reduction in patients experiencing a loss of both the central 4 points (Hazard ratio [HR]: 0.64, 95% CI: 0.44, 0.92) and the central 16 points (HR: 0.52. 95% CI: 0.32, 0.85) when compared to sham treated patients.

6.22 Although the results appear to support the claim of superior efficacy, it should be noted that it was not reported what the mean number of the central 4 or central 16 points the patients in each of the arms had already lost at baseline. As this was a post-hoc analysis and this was not a stratification factor, there is the potential for bias in these results.

6.23 Additionally, this analysis was carried out in the whole trial population for OAKS and as such included patients with subfoveal GA lesions. This does not align with the proposed PBS population which is restricted to patients with non-subfoveal lesions. The PSCR argued that despite the inclusion of patients with subfoveal lesions at baseline, microperimetry analyses still demonstrated a statistically significant reduction in patients experiencing a loss of both the central 4 points and the central 16 points.

6.24 To support the claim of superior efficacy for pegcetacoplan in the proposed PBS population, the submission provided a post-hoc subgroup analysis of patients with non-subfoveal GA lesions at baseline, pooling both the OAKS and DERBY trials. Non-subfoveal lesions were classified as ≥1µm away from the foveal central point.

6.25 This analysis was performed using data from month 24 whereas the primary outcome of CFB in total area of GA lesion size was measured at 12 months.

Table 6: Analyses of CFB in Total Area of GA Lesion(s) (mm2) in the Study Eye at Month 24 With MMRM Model in OAKS, DERBY, and Pooled Data by Study Eye GA Lesion Location at Baseline. mITT Population

Population	Pegcetacoplan every other month		Sham		
	n	LS mean (SE) CFB in lesion area, mm2	n	LS mean (SE) CFB in lesion area, mm2	Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm2
OAKS					
Non-subfoveal*	**73**	**4.29 (0.26)**	**59**	**5.18 (0.28)**	**-0.89 (-1.64, -0.15)**
Subfoveal	**131**	**2.76 (0.13)**	**147**	**3.54 (0.15)**	**-0.79 (-1.18, -0.39)**
DERBY					
Non-subfoveal*	**81**	**3.66 (0.19)**	**72**	**4.94 (0.33)**	**-1.28 (-2.04, -0.53)**
Subfoveal	**119**	**3.13 (0.18)**	**122**	**3.39 (0.16)**	**-0.27 (-0.73, 0.20)**
POOLED					
Non-subfoveal*	**154**	**3.92 (0.16)**	**131**	**5.03 (0.23)**	**-1.11 (-1.66, -0.57)**
Subfoveal	**250**	**2.90 (0.11)**	**269**	**3.46 (0.11)**	**-0.56 (-0.87, -0.26)**

Source: Table 30, pp145-146 of Attachment A2.8_DERBY_OAKS_Pooled summary of Clinical Efficacy.
CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Baseline is defined as the last available, non-missing observation prior to first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means.
Bold = statistically significant.
* The non-subfoveal subgroup aligns with the proposed PBS population for the treated eye.

6.26 The pooled data demonstrated a numerically greater treatment effect in participants with non-subfoveal involvement at baseline compared to those with subfoveal involvement at baseline.

6.27 For patients with non-subfoveal lesions at baseline, the observed mean change in lesion size was 3.92 mm^2 for pooled PEOM and 5.03 mm^2 for pooled sham, for a relative difference of −1.11 mm^2 (95% CI: −1.66, −0.57). This corresponds to a percentage difference of −22.1% for PEOM when compared to sham.

6.28 For patients with subfoveal lesions at baseline, the observed mean change in lesion size was 2.90 mm^2 for pooled PEOM and 3.46 mm^2 for pooled sham, for a relative

difference of -0.56 mm^2 (95% CI −0.87 to −0.26) for PEOM compared to sham. This corresponds to a percentage difference of −16.3% for PEOM when compared to sham.

6.29 The pooled results for PEOM in patients with non-subfoveal GA lesions at baseline for the outcome of CFB in GA lesion size supports the claim of superior efficacy for pegcetacoplan over BSC. However, results were not presented for functional outcomes in the non-subfoveal subgroup. As such, the extent of benefit to patients in terms of visual acuity is uncertain.

6.30 Additionally, the continuation criteria in the proposed PBS listing that patients must have non-subfoveal lesions (defined as lesions ≥1 µm from the foveal centre point) was not in the key trials. As such, the results from the trials may not represent clinical practice as patients in the trial may have continued pegcetacoplan despite developing subfoveal lesions. The PSCR stated that although the trial did not incorporate a stopping rule for incident subfoveal geographic atrophy (GA) lesions, subgroup analyses demonstrated significant benefit in patient with non-subfoveal lesions at baseline. The PSCR went on to state it was considered logical and evidence-based to conclude that treatment benefit is substantially reduced once the fovea is no longer intact. The ESC discussed that, as clinical assessment, visual acuity testing and Optical Coherence Tomography (OCT) will likely be performed whenever an intravitreal injection is administered, whether lesions remain non-subfoveal will be monitored. The pre-PBAC response stated clinical experts advised that OCT may not occur at every visit but patient assessment for ongoing treatment eligibility would be performed.

Comparative harms

A summary of key adverse events (AEs) for patients on treatment in DERBY and OAKS is presented in

6.31 Table 7. All AEs were considered treatment emergent if they either started after the first dose of pegcetacoplan or began before the dose but worsened in severity afterward.

Table 7: Summary of key adverse events in the trials

Trial ID	Pegcetacoplan pooled[a] n with event/ N (%)	Sham pooled n with event/N (%)	RD (95% CI)[b]	RR (95% CI)[b]
DERBY				
All AEs	358/414 (86.5)	169/206 (82.0)	0.04 (-0.02, 0.11)	1.05 (0.98, 1.14)
Study eye AEs	233/414 (56.3)	95/206 (46.1)	**0.10 (0.02, 0.19)**	**1.22 (1.03, 1.45)**
Fellow eye AEs	155/414 (37.4)	75/206 (36.4)	0.01 (-0.07, 0.09)	1.03 (0.83, 1.28)
Non-ocular	305/414 (73.7)	146/206 (70.9)	0.03 (-0.05, 0.10)	1.04 (0.94, 1.15)
AE severity				
Mild	106/414 (25.6)	56/206 (27.2)	-0.02 (-0.09, 0.06)	0.94 (0.71, 1.24)
Moderate	154/414 (37.2)	67/206 (32.5)	0.05 (-0.03, 0.13)	1.14 (0.91, 1.44)
Severe	98/414 (23.7)	46/206 (22.3)	0.01 (-0.06, 0.08)	1.06 (0.78, 1.44)
SAEs	112/414 (27.1)	54/206 (26.2)	0.01 (-0.07, 0.08)	1.03 (0.78, 1.36)
AEs of special interest in study eye				
nAMD	31/414 (7.5)	5/206 (2.4)	**0.05 (0.02, 0.08)**	**3.09 (1.22, 7.81)**
Increased IOP	7/414 (1.7)	3/206 (1.5)	0.01 (-0.02, 0.02)	1.16 (0.30, 4.44)
Intraocular inflammation	11/414 (2.7)	0/206 (0)	**0.03 (0.01, 0.04)**	-
Endophthalmitis	0/414 (0)	0/206 (0)	-	-
AEs related to treatment	50/414 (12.1)	8/206 (3.9)	**0.08 (0.04, 0.12)**	**3.11 (1.50, 6.44)**
AEs related to injection procedure	92/414 (22.2)	32/206 (15.5)	**0.07 (0.01, 0.13)**	1.43 (0.99, 2.06)
AEs leading to death	14/414 (3.4)	8/206 (3.9)	-0.01 (-0.04, 0.03)	0.87 (0.37, 2.04)
AEs leading to treatment discontinuation	30/414 (7.2)	14/206 (6.8)	0.01 (-0.04, 0.05)	1.07 (0.58, 1.97)
AEs leading to study discontinuation	28/414 (6.8)	15/206 (7.3)	-0.01 (-0.05, 0.04)	0.93 (0.51, 1.70)
OAKS				
All AEs	379/425 (89.2)	175/211 (82.9)	**0.06 (0.01, 0.12)**	**1.08 (1.00, 1.15)**
Study eye AEs	256/425 (60.2)	98/211 (46.4)	**0.14 (0.06, 0.22)**	**1.30 (1.10, 1.52)**
Fellow eye AEs	180/425 (42.4)	94/211 (44.5)	-0.02 (-0.10, 0.06)	0.95 (0.79, 1.15)
Non-ocular	339/425 (79.8)	154/211 (73.0)	0.07 (-0.01, 0.14)	1.09 (0.99, 1.20)
AE severity				
Mild	100/425 (23.5)	56/211 (26.5)	-0.03 (-0.10, 0.042)	0.89 (0.67, 1.18)
Moderate	153/425 (36.0)	75/211 (35.5)	0.01 (-0.08, 0.08)	1.01 (0.81, 1.26)
Severe	126/425 (29.6)	44/211 (20.9)	**0.09 (0.02, 0.16)**	**1.42 (1.05, 1.92)**
SAEs	141/425 (33.2)	58/211 (27.5)	0.06 (-0.02, 0.13)	1.21 (0.93, 1.56)
AEs of special interest in study eye				
nAMD	34/425 (8.0)	3/211 (1.4)	**0.07 (0.04, 0.10)**	**5.63 (1.75, 18.11)**
Increased IOP	13/425 (3.1)	0/211 (0)	0.03 (0.01, 0.05)	-
Intraocular inflammation	13/425 (3.1)	1/211 (0.5)	0.03 (0.01, 0.05)	6.45 (0.85, 49.01)
Endophthalmitis	5/425 (1.2)	0/211 (0)	0.01 (0.01, 0.022)	-
AEs related to treatment	44/425 (10.4)	11/211 (5.2)	**0.05 (0.01, 0.09)**	**1.99 (1.05, 3.77)**
AEs related to injection procedure	112/425 (26.4)	41/211 (19.4)	**0.07 (0.01, 0.14)**	1.36 (0.99, 1.86)
AEs leading to death	29/425 (6.8)	8/211 (3.8)	0.03 (-0.01, 0.07)	1.80 (0.84, 3.87)
AEs leading to treatment discontinuation	49/425 (11.5)	14/211 (6.6)	0.05 (0.01, 0.09)	1.74 (0.98, 3.07)
AEs leading to study discontinuation	48/425 (11.3)	14/211 (6.6)	0.05 (0.01, 0.09)	1.70 (0.96, 3.02)

Source: Table 63, p147, and Table 65, pp149-150 of the submission.

AE = adverse event; CI = confidence interval; IOP = intraocular pressure; n = number of subjects; N = total number of subjects in the group; nAMD = Neovascular age-related macular degeneration; RD = risk difference; RR = risk ratio; SAEs = serious adverse events

[a] Safety for pegcetacoplan included the pooled results of both monthly and every other monthly administration as this aligns with what the submission used for Sham safety.
[b] Calculated during the evaluation
Bold = statistically significant

6.32 Overall, there was a higher reported incidence of AEs (including ocular AEs) in the pegcetacoplan treated groups compared to the sham injection groups, including AEs of special interest such as increased intraocular pressure, intraocular inflammation (including endophthalmitis) and neovascular age related macular degeneration (nAMD). In both OAKS and DERBY, 2 and 3 times (respectively) more AEs related to treatment were recorded in the pegcetacoplan groups compared to sham groups. Additionally, the sponsor has received reports of six cases of vasculitis in the post-marketing setting in the US which are currently being investigated.

6.33 While AE severity was generally balanced between groups in DERBY, pegcetacoplan treated groups in OAKS recorded more severe AEs compared to sham (29.6% vs 20.9%).

6.34 The ESC noted an analysis of post-marketing cases of retinal vasculitis after intravitreal pegcetacoplan undertaken by the American Society of Retina Specialists (ASRS) Research and Safety in Therapeutics (ReST) Committee in which an expert panel performed a retrospective review of cases of retinal vasculitis reported to the ASRS.[7] The analysis found that 14 eyes of 13 patients were confirmed to have retinal vasculitis by review of imaging studies with all cases occurring after the first pegcetacoplan injection. The ESC considered that there remained a real-world risk of retinal vasculitis, albeit rare at an estimated rate per injection of approximately 0.01%. The ESC noted that in the post market setting until 14 February 2025, an estimated 80,776 patients have been exposed to pegcetacoplan by the IVT route, representing an estimated 71,741.3 patient years.

6.35 The sponsor made a claim of manageable safety for pegcetacoplan compared to BSC. Although the AEs associated with pegcetacoplan may be manageable, this statement is not informative regarding the comparative safety of the two interventions. The ESC agreed with the evaluation that, from the evidence presented in the submission, a claim of inferior safety for pegcetacoplan compared to sham is appropriate.

Benefits/harms

6.36 A summary of the comparative benefits and harms for PEOM versus sham injections is presented in Table 8.

[7] Witkin AJ, Jaffe GJ, Srivastava SK, Davis JL, Kim JE. 2023. Retinal vasculitis after intravitreal pegcetacoplan: Report from the ASRS Research and Safety in Therapeutics (ReST) Committee. J Vitreoretin Dis. 8(1):9-20.

Table 8: Summary of comparative benefits and harms for pegcetacoplan and sham

Benefits							
CFB in total Area of GA Lesions (mm2) in the study eye at month 24 with MMRM – non-subfoveal subgroup							
	Pegcetacoplan every other month			**Sham pooled**			**Difference (95% CI) in LS mean CFB in lesion area vs sham pooled group, mm2**
	N	**Mean Δ baseline**	**SE**	**N**	**Mean Δ baseline**	**SE**	
OAKS	73	4.29	0.26	59	5.18	0.28	**-0.89 (-1.64, -0.15)**
DERBY	81	3.66	0.19	72	4.94	0.33	**-1.28 (-2.04, -0.53)**
Pooled	154	3.92	0.16	131	5.03	0.23	**-1.11 (-1.66, -0.57)**
Change from baseline in NL-BCVA score (ETDRS letters) at month 24 (mITT)							
OAKS	205	−8.53	1.05	207	−7.66	1.07	−0.87 (−3.79, 2.06)
DERBY	201	−8.95	1.03	195	−6.22	1.02	−2.73 (−5.57, 0.11)
Conversion of all 4 or all 16 central microperimetry points to scotoma in the study eye in OAKS from baseline through to month 24 (mITT)							
	Pegcetacoplan every other month n/N (%)			**Sham n/N (%)**			**Hazard ratio (95% CI) P value**
Conversion of all 4 central points	59/152 (38.8%)			64/146 (43.8%)			**0.64 (0.44-0.92)**
Conversion of all 16 central points	28/184 (15.2%)			39/181 (21.5%)			**0.52 (0.32-0.85)**

Harms						
	Pegcetacoplan pooled[b]	**Sham pooled**	**RR (95% CI)[c]**	**Event rate/100 patients[d]**		**RD (95% CI)[c]**
				pegcetacoplan	**Sham**	
AEs related to treatment						
DERBY	50/414 (12.1%)	8/206 (3.9%)	**3.11 (1.50, 6.44)**	12	4	**0.08 (0.04, 0.12)**
OAKS	44/425 (10.4%)	11/211 (5.2%)	**1.99 (1.05, 3.77)**	10	5	**0.05 (0.01, 0.09)**
Pooled	94/839 (11.2%)	19/417 (4.6%)	**2.46 (1.52, 3.97)**	11	5	**0.07 (0.04, 0.10)**
nAMD (study eye)						
DERBY	31/414 (7.5%)	5/206 (2.4%)	**3.09 (1.22, 7.82)**	8	2	**0.05 (0.02, 0.08)**
OAKS	34/425 (8.0%)	3/211 (1.4%)	**5.63 (1.75, 18.11)**	8	1	**0.07 (0.04, 0.10)**
Pooled	65/839 (7.8%)	8/417 (1.9%)	**4.04 (1.96, 8.34)**	8	2	**0.06 (0.04, 0.08)**

Source: Table 30, pp145-146 of Attachment A2.8_DERBY_OAKS_Pooled summary of Clinical Efficacy Table 63, p147, and Table 65, pp149-150 of the submission.

CI = confidence interval; CFB = change from baseline; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; n = number of patients with event; N = number of patients in group; RD = risk difference; RR = risk ratio; SE = standard error.

[a] The NL-BCVA and microperimetry data was in the mITT population rather than the non-subfoveal GA lesions subgroup that aligns with the proposed PBS population.

[b] Safety for pegcetacoplan included the pooled results of both monthly and every other monthly administration as this aligns with what the submission used for Sham safety. Efficacy for pegcetacoplan is only informed by the every-other-monthly administration as this aligns with the approved product information.

[c] Calculated during the evaluation using StataMP18

[d] Maximum duration of follow-up in OAKS and DERBY was 24 months.

Bold = statistically significant

6.37 On the basis of direct evidence presented by the submission, the comparison of pegcetacoplan every other month and sham injections over a maximum duration of exposure of 24 months resulted in:

- Approximately a 1.11 mm^2 (22.1%) smaller total area of GA lesion growth in patients with non-subfoveal lesions at baseline.
- Approximately 5 less patients would experience a loss of the central 4 microperimetry points to GA lesion (for every 100 patients treated with pegcetacoplan in comparison with sham injections).
- Approximately 6 less patients would experience a loss of the central 16 microperimetry points to GA lesion (for every 100 patients treated with pegcetacoplan in comparison with sham injections).
- Approximately 7 additional patients would experience an adverse event related to treatment (for every 100 patients treated with pegcetacoplan in comparison with sham injections).
- Approximately 6 additional patients would develop nAMD in the treated eye (for every 100 patients treated with pegcetacoplan in comparison with sham injections).

Clinical claim

6.38 The submission described pegcetacoplan as superior in terms of effectiveness compared to sham injection. The ESC agreed with the evaluation that this claim was adequately supported but the magnitude of the benefit was uncertain. The key issues were that although the submission demonstrated that pegcetacoplan dosed every other month in patients with non-subfoveal GA lesions at baseline slowed the growth of the GA lesions, the submission did not demonstrate a difference in functional outcomes, such as BCVA, in the proposed PBS population. The ESC noted that the submission assumed anatomical preservation will result in better functional vision and considered that this was reasonable but not proven in any functional measure. Hence, while pegcetacoplan may slow the progression of GA lesion growth, the ESC considered it is highly uncertain how this will translate into a delay in loss of visual acuity for patients.

6.39 The submission described pegcetacoplan as manageable in terms of safety compared to sham. This claim was not an appropriate safety claim as the submission did not make a comparative safety claim for pegcetacoplan compared to sham. Based on the presented evidence, pegcetacoplan has inferior safety compared to sham injection with a higher rate of adverse events related to treatment (12.1% vs. 3.9% in DERBY) and a higher rate of nAMD (7.5% vs. 2.4% in DERBY). The PSCR acknowledged the higher rate of adverse events and stated that the proposed PBS population is intended to reflect a group in whom the expected treatment benefits outweigh these risks. The ESC considered a claim of inferior safety was appropriate.

6.40 The PBAC considered that the claim of superior comparative effectiveness was reasonable but the magnitude of the effect on delaying vision loss was uncertain.

6.41 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.42 The submission presented a modelled economic evaluation based on direct randomised trials, DERBY and OAKS. The economic model assessed pegcetacoplan compared to BSC in patients with GA secondary to AMD for patients with non-subfoveal lesions in their best seeing eye. The evaluation considered that the clinical claim of superior effectiveness for pegcetacoplan compared to BSC, in patients with non-subfoveal lesions (i.e. the proposed PBS patient population) in terms of functional outcomes was not established (see paragraph 6.38). The ESC agreed with the evaluation that, while pegcetacoplan may slow the progression of GA lesion growth, it was highly uncertain how this will translate into a delay in loss of visual acuity for patients. The ESC advised the model structure was not reliable for decision-making due to concerns associated with the quantification of this surrogate functional outcome relationship and the estimated treatment effect. The pre-PBAC response stated that microperimetry is a sensitive and precise measure of retinal function that better reflects the structural preservation of the retina associated with pegcetacoplan and argued that this was the best evidence of possible benefit in functional outcomes. This argument was also supported by the sponsor hearing (see paragraph 6.1).

6.43 Table 9 summarises the key components of the economic evaluation.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Pegcetacoplan versus BSC.
Time horizon	20 years (versus 24 month follow up in the DERBY and OAKS trials).
Outcomes	Quality-adjusted life years.
Methods used to generate results	Markov cohort.
Health states	Defined by number of ETDRS letters: ≥ 76, 75-66, 65-51, 50-36 and ≤ 35 letters and dead.
Cycle length	12 weeks.
Transition probabilities	In the BSC arm, disease progression transition probabilities were informed by an analysis of patients in the control arms of the DERBY and OAKS trials. In the pegcetacoplan arm, a treatment effect (applied as a relative risk reduction) was derived from KM data for the event of central 16 absolute scotomatous points and was applied to BSC transition probabilities. Mortality was informed by ABS lifetables in both arms. This evaluation considered this was reasonable.
Extrapolation method	The submission assumed BSC transitions would remain constant until the end of the time horizon. The evaluation considered this was uncertain. The pegcetacoplan treatment effect was assumed to increase and continue without any waning while patients remained on treatment (which was until they enter the ≤ 35 letters health state or death) based on an observed increasing treatment effect during the trials. This was not associated with any observation of increasing functional effect. The submission assumed patients will not develop subfoveal lesions and hence would receive continual treatment with pegcetacoplan. However, this is inconsistent with the natural disease course where patients would eventually develop subfoveal lesions and would become ineligible to access PBS-subsidised pegcetacoplan.
Health related quality of life	Identical across the two arms, sourced from a published ranibizumab economic model which reports utilities for ETDRS letter groups and no disutilities for AEs or pegcetacoplan administrations were applied. Assuming identical utilities across the two treatment arms was uncertain given AEs associated with pegcetacoplan over BSC.
Costs	The number of pegcetacoplan injections per year were derived from the DERBY and OAKS trials. The submission assumed that patients who completed the trial had full treatment compliance, and that patients who did not complete the full 24 months received nil injections. The evaluation considered this was not appropriate. Costs included aged care residency, HCP and CHSP costs. The entirety of these costs may not constitute direct medical costs and therefore should be excluded from the base case analysis.

Source: Constructed during the evaluation from the "A3.1_Pegcetacoplan PBAC CE model submission 2025 vF" attachment provided with the submission.
AEs = adverse events; BCVA = best corrected visual acuity; BSC = best supportive care; CHSP = Commonwealth Home Support Program; ETDRS = Early Treatment Diabetic Retinopathy Study; HCP = Home Care Package; KM = Kaplan Meier; PBS = Pharmaceutical Benefits Scheme; QALYs = quality adjusted life year.

6.44 The model adopts a 20-year time horizon. The duration of follow-up for the DERBY and OAKS trial was just 24 months, and there is no additional comparative external data to inform disease progression beyond this time period. Therefore, the evaluation considered the extrapolations in the model were highly uncertain. The PSCR stated that the GALE extension study supports that the effectiveness of pegcetacoplan is maintained until at least 4 years (with 5-year data expected). The ESC agreed with the PSCR that the GALE extension study provided some noncomparative support for ongoing effect but still considered extrapolation of treatment effect for the duration of therapy (up to 20 years) remained highly uncertain. The ESC noted the incremental cost-effectiveness ratio (ICER) was sensitive to the time horizon (see Table 13). The

ESC also did not consider 20 years a reasonable time horizon in this patient population; the starting age in the model is 72 years and, whilst treatment may slow lesion growth, the disease will continue to progress.

6.45 The structure of the economic model relied on the progression of vision loss classified by health states grouped by Early Treatment Diabetic Retinopathy Study (ETDRS) letters. In the BSC arm, transitions (which were not time dependent) were informed by an analysis of the sham arms of the DERBY and OAKS trials and assumed to continue until the end of the time horizon. This was highly uncertain.

6.46 The submission assumed that the central 16 scotomatous points analysis was a surrogate for BCVA outcomes and accordingly translated this outcome in terms of BCVA. Notwithstanding the issues already raised above regarding the microperimetry analysis (see paragraphs 6.22 and 6.23), additional concerns associated with the quantification of the surrogate functional outcome relationship and the estimated treatment effect include:

- Change in ETDRS letters was measured in the trial, and the submission does not adequately justify why observed BCVA data were not used directly. The ESC noted the modelled treatment effect in terms of ETDRS letters is considerably greater than the observed effect. The pre-PBAC response acknowledged that there was no significant difference in BCVA between treatment arms in the trials. However, the pre-PBAC response continued to argue that functional outcome measures such as BCVA have limited validity in comprehensively assessing treatment impacts in GA. In addition, the pre-PBAC response noted that the clinical trials included a mixed population of patients with non-subfoveal (35%) and subfoveal (65%) GA and argued that the treatment effect is expected to be greater in the proposed PBS population where the fovea remains intact.
- The outcome measure of time to 'central 16 scotomatous points' is not applicable for the proposed PBS listing, since patients will often experience subfoveal lesions before experiencing central 16 scotomatous points; and have to stop treatment (whereas in the trial treatment is continued). Therefore, the treatment effect in the trial is unlikely to be realised for many patients in the proposed PBS population. The evaluation considered the treatment effect and cost of pegcetacoplan are therefore overestimated for the proposed listing. The evaluation considered the time to experiencing central 4 scotomatous points, which was also presented in the analysis, would be a better estimate of the pegcetacoplan treatment in the proposed PBS population as the fovea centre is most closely approximated by the central four points. However, the evaluation considered this measure may still overestimate the treatment effect as patients may still experience subfoveal lesions before experiencing central 4 scotomatous points. The PSCR acknowledged that the time to central 4 scotomatous points may provide an approximation of foveal involvement, as these points lie immediately adjacent to the fovea centre. The PSCR noted that

the central 16 points includes both the central 4 and the surrounding 12 points and argued that the use of the central 16 points outcome better captured the preventive effects of pegcetacoplan on central vision loss. The ESC considered that it was unclear what the direction of bias in the ICER would be with the use of the central 4 scotomatous points and advised that use of either of these endpoints would not resolve underlying concerns regarding the surrogate outcome measure.

- Similarly, the submission assumes that PBS subsidised pegcetacoplan treatment is ongoing until patients enter the ≤ 35 letters health state or die. This also implicitly assumes that patients will not develop subfoveal lesions before such time, which is inconsistent with the natural disease course. The structural design of the model did not allow rectification of this issue during the evaluation. The PSCR argued that as subfoveal lesions are strongly correlated with poorer visual acuity on the BCVA scale, the model accounted for treatment discontinuation using ≤ 35 letters as a proxy for subfoveal GA progression. The PSCR stated that as ≤ 35 letters equates to legal blindness patients have no further vision to preserve and are not expected to derive further treatment benefit.

- The model assumes the full treatment effect is ongoing for the duration of therapy (up to 20 years). No long-term evidence is provided to support this claim (e.g. long-term data with ongoing reduction in scotomatous points, long-term data on BCVA improvement, nor evidence the suggested surrogate-outcome relationship can be extrapolated). As outlined in paragraph 6.44, the ESC agreed with the PSCR that the GALE extension study supported the effectiveness of pegcetacoplan being maintained out to 4 years for GA lesion growth (see paragraph 6.16). However, the ESC considered extrapolation of treatment effect for the duration of therapy which is up to 20 years remained highly uncertain.
    - There is no evidence to suggest an ongoing treatment effect after patients experience 16 or 4 absolute scotomatous points. If the link between a loss of all 16 or 4 absolute scotomatous points and a loss of 12 – 13 ETDRS letters (approximately one health state) is accepted, once a patient loses all 16 or 4 central points, it would inform one transition. After this, patients should cease treatment and return back to BSC transition probabilities as there they are no longer eligible for pegcetacoplan and there is no evidence for an ongoing treatment effect beyond treatment cessation. The ESC noted that a publication from the OAKS trial, Chakravarthy et al. (2025), reported only a small difference in the ETDRS letters loss between losing the central 16 versus 4 scotomatous points (-12.7 and -11.7 letters, respectively). The ESC agreed with

the evaluation that this implies that once patients experience central 4 scotomatous points, there is minimal ongoing change in BCVA.[8]

6.47 The utility values applied in the economic model differed by health state but were not treatment specific. No quality adjusted life year (QALY) decrements were applied for pegcetacoplan intravitreal injections or AEs. The ESC considered that this was not justified and not likely to be reasonable given the adverse events associated with pegcetacoplan over BSC. The ICER was sensitive to differences in utilities across the two arms (see Table 13).

6.48 Health state utility values were based off an external time trade-off analysis conducted by Czoski-Murray et al. (2009)[9]. This study used contact lenses in both eyes to simulate visual impairment caused by age-related macular degeneration to elicit time trade-offs from the general population of the United Kingdom. The contact lenses were designed to simulate different Visual Acuity Logarithm of the Minimum Angle of Resolution (VALogMAR) groups, and a regression analysis was conducted to relate VALogMAR to utility values. The submission relied on another study which converted the VALogMAR scores to ETDRS letters and used those utilities in the economic model.**Error! Bookmark not defined.** This was generally reasonable.

6.49 To estimate the number of pegcetacoplan injections per year, the submission had multiplied the proportion of patients who completed the full 24-month treatment duration in the key trials by the number of planned doses for that 24-month period (12). This essentially assumed that patients who completed the trial had full treatment compliance, and that patients who did not complete the full 24 months received nil injections. The ESC agreed with the evaluation that this was not reasonable. Using the treatment compliance reported in the trials multiplied by the number of scheduled doses resulted in a dose frequency of once every 68 days (versus once every 76 days in the base case and once every 60 days in the PI).

6.50 The submission also included aged care related costs, including costs associated with aged care residency, Home Care Packages (HCP) and the Commonwealth Home Support Program (CHSP). These costs, especially HCP and CHSP costs, may not constitute direct medical costs and hence should be excluded from the base case analysis. The PSCR argued that residential care and home care packages are included in the PBAC Manual of Resources (2016) and therefore should be included in the base case analysis. The ESC acknowledged the inclusion of such costs in the PBAC Manual of Resources (2016) but considered it was hard to quantify the proportion of these costs that were encompassed by the manual definition. The ESC considered that the aged care related costs in the economic model included both aspects of health and

[8] Chakravarthy U, Schwartz R, Guymer RH, Holz FG, Rachitskaya AV, Vujosevic S, et al. Visual Function Benefit After Treatment With Pegcetacoplan: Microperimetry Analysis From the Phase 3 Oaks Trial. American Journal of Ophthalmology. 2025;273:119-29.

[9] Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing Condition-Specific Health States Using Simulation Contact Lenses. Value in Health. 2009;12(5):793-9.

non-health care and that these were very hard to disentangle in the model. The ESC noted that excluding HCP and CHSP costs increased the ICER by [redacted]% (from $35,000 to < $45,000 per QALY gained to $95,000 to < $115,000 per QALY gained).

6.51 The key model drivers are presented in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Choice of outcome measure	The treatment effect derived from the time to central 16 scotomatous points microperimetry analysis of the OAKS trial. The evaluation considered that this was not an appropriate outcome measure for the proposed PBS population. Patients can experience subfoveal lesions before experiencing the central 16 scotomatous points and hence in clinical practice would have to cease treatment (as per the proposed PBS criteria) but in the trial patients were able to continue treatment. The ESC considered that there were underlying concerns regarding the surrogate outcome measure used in the economic model (see paragraph 6.46).	High, favours pegcetacoplan.
Ongoing treatment utilisation and treatment effect	Pegcetacoplan treatment and its treatment effect was assumed to continue until patients ceased treatment which was when they entered the ≤ 35 letters health state or died. This assumes that modelled patients will not develop subfoveal lesions and hence would receive continual treatment. However, this is inconsistent with the natural disease course where patients would eventually experience subfoveal lesions and therefore will be ineligible to access pegcetacoplan. The effect of treatment discontinuation and therefore the loss of a treatment effect for patients experiencing subfoveal lesion could not be explored with the model's structure. The PSCR stated that as ≤ 35 letters equates to legal blindness patients have no further vision to preserve and are not expected to derive further treatment benefit.	Impact unknown.
Aged care costs	The base case analysis includes aged care related costs, including costs associated with aged care residency, HCP and CHSP. These costs, especially HCP and CSHP costs may not constitute direct medical costs and hence should be excluded from the base case analysis. The ESC noted the PSCR argument that residential care and home care packages are included in the PBAC Manual of Resources (2016) and advised that both health and non-health care related costs were included in the aged care related costs modelled. The ESC considered that the health and non-health care related costs were hard to separate in the model.	High, favours pegcetacoplan. Excluding HCP and CSHP costs increased the ICER by [redacted]%.
Pegcetacoplan treatment compliance	The submission had multiplied the proportion of patients who completed the full 24-month treatment duration in the key trials by the number of planned doses for that 24 month period (12) to estimate pegcetacoplan treatment compliance. This essentially assumed that patients who completed the trial had full treatment compliance, and that patients who did not complete the full 24 months received nil injection.	High, favours pegcetacoplan. Using the treatment compliance from the key trials increased the ICER by [redacted]%.

Source: Constructed during the evaluation from the "A3.1_Pegcetacoplan PBAC CE model submission 2025 vF" attachment provided with the submission.

CHSP = Commonwealth Home Support Program; HCP = Home Care Package; ICER = incremental cost-effectiveness ratio; PBS = Pharmaceutical Benefits Scheme; QALY = quality-adjusted life year

The redacted values correspond to the following ranges:

[1] *$45,000 to < $55,000*

6.52 The submission did not present a stepped economic evaluation. This was not reasonable given the model is highly sensitive to extrapolations and external assumptions. The evaluation has conducted a stepped analysis, starting from a

trial-based analysis through to the full modelled evaluation (see Table 11). The ESC noted the model estimates a much greater difference in visual acuity between the treatment arms at 24 months (step 2) than the trials (step 1). As mentioned in paragraph 6.46, the ESC agreed with the evaluation that this raises considerable uncertainty regarding the validity of the surrogate and how it is applied in the model.

Table 11: Results of the stepped economic evaluation conducted during the evaluation

Step and component	Pegcetacoplan	BSC	Increment
Step 1: 24 month time horizon, based on BCVA outcomes in the trials[a]			
Costs	$	$26,841	$
Observed ETDRS letters lost	8.73	6.95	1.78
Incremental cost/ETDRS letter saved			$ [1]
Step 2: Switch to simulated BCVA outcomes based on microperimetry analysis, 24 month time horizon			
Costs	$	$26,841	$
Modelled ETDRS letters lost[b]	-19.81	-25.80	5.96
Incremental cost/ ETDRS letter saved			$ [2]
Step 3: Converting BCVA to utilities and extrapolate out to 20 years, 5% discounting (base case)			
Costs	$	$255,719	$
QALYs	4.72	4.46	0.26
Incremental cost/QALY gained			**$** [3]

Source: Constructed during the evaluation from the "A3.1_Pegcetacoplan PBAC CE model submission 2025 vF" attachment provided with the submission.

BCVA = best corrected visual acuity; BSC = best supportive care; ETDRS = Early Treatment Diabetic Retinopathy Study; mITT = modified intent to treat; QALY = quality-adjusted life year

[a] Based on the mITT populations of DERBY and OAKS, weighted by the number of patients in each trial.

[b] Simulated BCVA outcomes based on the submission's surrogate outcome (time to central 16 scotomatous points)

The redacted values correspond to the following ranges:

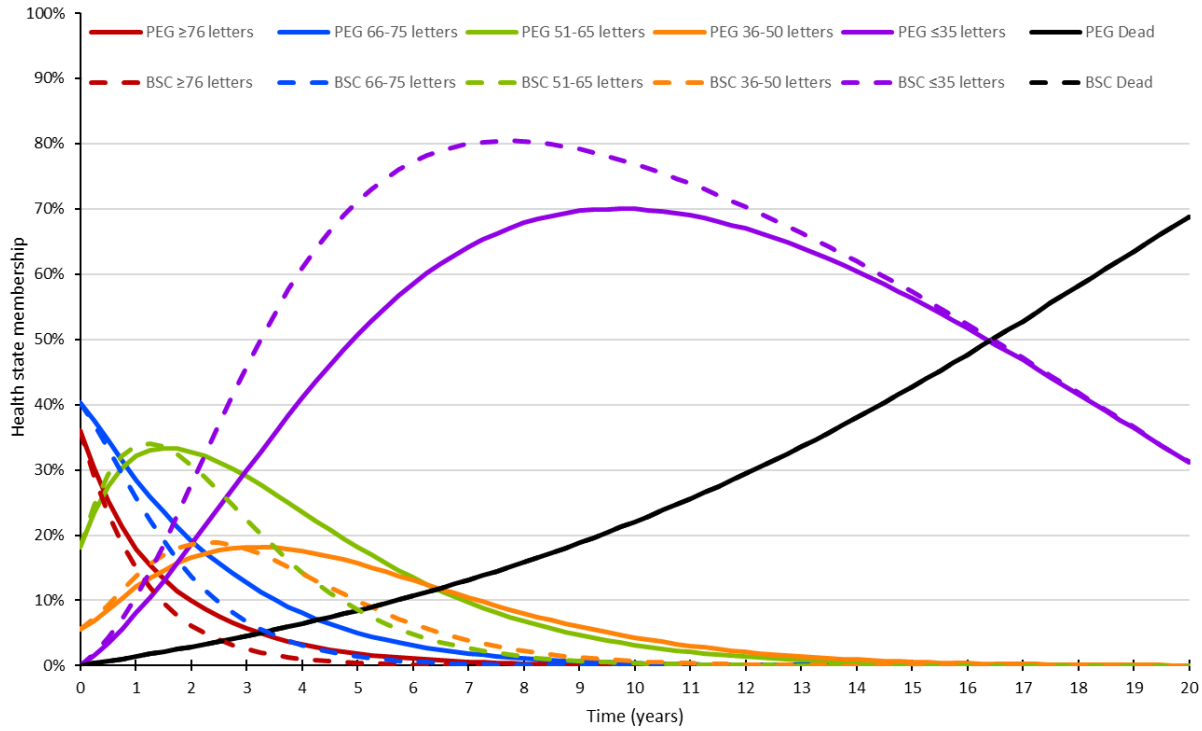
[1] *$5,000 to < $15,000*

[2] *$0 to < $5,000*

[3] *$45,000 to < $55,000*

6.53 Markov traces were constructed during the evaluation (see Figure 1). Membership in the pegcetacoplan ≤35 letters health state never reaches the same proportion of patients in the BSC arm, most likely because pegcetacoplan delays progression so many patients die before reaching this health state. Prevention of progression to this health state (associated with low utilities and high costs) is a significant model driver.

Figure 1: Health state membership over the time horizon



Source: Constructed during the evaluation from the "A3.1_Pegcetacoplan PBAC CE model submission 2025 vF" attachment provided with the submission.
BSC = best supportive care; PEG = pegcetacoplan

6.54 The disaggregated and aggregated costs and outcomes are presented in Table 12. Pegcetacoplan costs make up the majority of the incremental costs between the two arms. Health state costs for the 51-65 and 36-50 letters health state also make up substantial incremental costs, as pegcetacoplan patients spend longer times in these health states than BSC patients. The ESC noted that most cost savings result from delaying or avoiding entirely pegcetacoplan patients entering the ≤35 letters health state, which has high costs compared to the other health states. As such the ESC advised that this health state was highly dependent on baseline transition to it and its costing. The ESC considered that the baseline transitions produced estimates that lacked face validity, with the modelled treatment effect considerably greater than the observed benefit (see paragraph 6.46) and noted that the costing included non-health costs (see paragraph 6.50). The ESC noted that consistent with the costs, most of the incremental QALYs are accrued in ≥76 letters, 66-75, 51-65 and the 36-50 letters health state in the pegcetacoplan arm.

Table 12: Disaggregated summary of cost and outcome impacts

Costs	Pegcetacoplan	BSC	Incremental	%
Treatment costs				
Pegcetacoplan acquisition	$[redacted]	$0	$[redacted]	[redacted]%
Pegcetacoplan administration	$6,333	$0	$6,333	54%
Adverse event costs	$1,793	$1,447	$346	3%
Health state costs (disease management, aged care and hospitalisation)				
≥76 letters	$4,162	$3,068	$1,094	9%
66-75 letters	$8,628	$6,312	$2,316	20%
51-65 letters	$21,063	$15,378	$5,685	48%
36-50 letters	$21,037	$15,616	$5,421	46%
≤35 letters	$181,032	$213,897	-$32,865	-280%
Total	$[redacted]	$255,719	$[redacted]	100%
Outcomes – LYs (undiscounted)				
≥76 letters	0.57	0.41	0.16	N/A
66-75 letters	1.01	0.71	0.29	
51-65 letters	1.90	1.31	0.59	
36-50 letters	1.34	0.93	0.41	
≤35 letters	9.88	11.34	-1.46	
Total	14.70	14.70	0.00	
Outcomes – QALYs (discounted)				
≥76 letters	0.43	0.31	0.11	43%
66-75 letters	0.62	0.45	0.17	64%
51-65 letters	0.94	0.68	0.25	97%
36-50 letters	0.52	0.38	0.13	51%
≤35 letters	2.22	2.63	-0.40	-155%
Total	4.72	4.46	0.26	100%

Source: Constructed during the evaluation from the "A3.1_Pegcetacoplan PBAC CE model submission 2025 vF" attachment provided with the submission.
BSC = best supportive care; LYs = life years; QALYs= quality-adjusted life year.

6.55 Key sensitivity analyses performed during the evaluation are presented in Table 13. The additional multivariate sensitivity analyses requested by the PBAC are also presented in Table 13. The PBAC requested multivariate analyses that reduced the time horizon to 15 years along and included a utility decrement due to pegcetacoplan administration. In addition, the PBAC requested analyses which revised inputs for the treatment effect beyond the observed period, the number of pegcetacoplan injections and the HCP and CHSP costs. The PBAC noted that multivariate analyses that incorporated each of these inputs increased the base case ICER from $45,000 to < $55,000 per QALY gained to $95,000 to < $115,000 per QALY gained. The PBAC acknowledged that incorporating aflibercept and ranibizumab effective prices would further impact the ICER (data not shown).

Table 13: Key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% Change
Base case	$[redacted]	0.261	$[redacted][1]	0%
Discount rate (base case: 5% costs and outcomes)				
• 0% costs and outcomes	$[redacted]	0.337	$[redacted][2]	-[redacted]%
• 3.5% costs and outcomes	$[redacted]	0.281	$[redacted][3]	-[redacted]%
Time horizon (base case: 20 years)				
• 10 years	$[redacted]	0.245	$[redacted][1]	[redacted]%
• 15 years #1	$[redacted]	0.260	$[redacted][1]	[redacted]%
Treatment effect beyond the observed period (base case: RRR of 0.35)				
• RRR of 0.32 (the same as the end of the observed period) #2	$[redacted]	0.240	$[redacted][1]	[redacted]%
• RRR of 0.00	$[redacted]	0.104	$[redacted][4]	[redacted]%
Difference in utilities across the two treatment arms (base case: no difference)				
• Utilities in the pegcetacoplan arm 5% lower than BSC (except for the ≤35 letters health state)	$[redacted]	0.136	$[redacted][5]	[redacted]%
Utility decrement due to pegcetacoplan administration				
• 100% utility loss for one day for 50% of patients per administration (NICE recommendation[a]) #3	$[redacted]	0.244	$[redacted][1]	[redacted]%
Number of pegcetacoplan injections per year (base case: 4.71)				
• 5.39 (applying treatment compliance from the key trials) #4	$[redacted]	0.261	$[redacted][6]	[redacted]%
Aged care costs (base case: included)				
• Exclude HCP costs	$[redacted]	0.261	$[redacted][7]	[redacted]%
• Exclude CHSP costs	$[redacted]	0.261	$[redacted][1]	[redacted]%
• Exclude institutionalisation costs	$[redacted]	0.261	$[redacted][1]	[redacted]%
• Exclude both HCP and CHSP	$[redacted]	0.261	$[redacted][7]	[redacted]%
• Exclude HCP, CHSP and institutionalisation costs	$[redacted]	0.261	$[redacted][8]	[redacted]%
• HCP and CHSP costs reduced by 50% #5	$[redacted]	0.261	$[redacted][5]	[redacted]%
Multivariate analyses				
#1 and #2	$[redacted]	0.239	$[redacted][1]	[redacted]%
#1, #2 and #3	$[redacted]	0.222	$[redacted][6]	[redacted]%
#1, #2, #3 and #4	$[redacted]	0.220	$[redacted][5]	[redacted]%
#1, #2, #3, #4 and #5	$[redacted]	0.220	$[redacted][7]	[redacted]%

Source: Constructed during the evaluation from the "A3.1_Pegcetacoplan PBAC CE model submission 2025 vF" attachment provided with the submission.

AE = adverse event; BSC = best supportive care; CHSP = Commonwealth Home Support Package; HCP = Home Care Package; ICER = incremental cost effective ratio; OCT = Optical Coherence Tomography; QALY = quality-adjusted life year; RRR = relative risk reduction

[a] NICE guideline NG82; Appendix J: Health Economics.

The redacted values correspond to the following ranges:

[1] *$45,000 to < $55,000*
[2] *$25,000 to < $35,000*
[3] *$35,000 to < $45,000*
[4] *$155,000 to < $255,000*
[5] *$75,000 to < $95,000*
[6] *$55,000 to < $75,000*
[7] *$95,000 to < $115,000*
[8] *$115,000 to < $135,000*

Drug cost/patient/year

6.56 The drug costs per patient are presented in Table 14. There were significant differences between the number of injections per year in the trial versus the model versus the financial estimates. This was not appropriate and the evaluation conducted a sensitivity analyses using the trials' mean number of injections per year.

Table 14: Pegcetacoplan cost per patient for proposed and comparator drugs

	DERBY and OAKS	Economic Model	Financial estimates
Mean number injections per year	5.39[a]	4.71[b]	**4.5**[c]
Cost per injection		$ [redacted]	
Cost/patient/year	$ [redacted]	$ [redacted]	$ [redacted]

Source: Constructed during the evaluation from the "A3.1_Pegcetacoplan PBAC CE model submission 2025 vF" attachment provided with the submission.

[a] Assuming treatment compliance rates of 89% and 91% from the DERBY and OAKS trials, respectively, weighted by the number of patients in each trial and multiplied by the number of scheduled injections (6).

[b] The submission assumed patients who completed the 24 months trials (79%) had full treatment compliance and patients who did not complete the trial had received no injections. Halved to get the annual number of injections.

[c] In the financial analysis, the submission further adjusted its base case number of injections per year by a treatment compliance rate (95.5%).

Estimated PBS usage & financial impacts

6.57 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the number of prevalent patients who would be eligible for the proposed pegcetacoplan treatment. A summary of the data sources and parameter values used to estimate the utilisation and financial impacts associated with the proposed listing of pegcetacoplan for the treatment of GA is shown in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent population	Prevalence of 1.29% (patients aged 60 years and older) based on late AMD and the proportion of patients with GA as reported in Australian National Eye Health Survey (NEHS).	The evaluation considered this was appropriate and confirmed the method of calculation has been verified. DUSC considered this approach was reasonable.
Proportion of patients meeting PBS criteria	Proportion of patients with bilateral GA – 63.5% (IRIS) and proportion of patients with non-subfoveal GA in one eye and subfoveal GA in the fellow eye 33.9% (FRB!)	The IRIS data is an appropriate large-scale data source. DUSC considered this was reasonable. The FRB! is recent data (starting in 2023) using the Australian cohort. While noting that the cohort is small (20 out of 59 patients), it appears to be an appropriate data source for this very targeted intervention. DUSC considered this input to be a possible overestimate, recognising that there is no other reliable source.

Parameter	Value applied and source	Comment
Uptake rate	[redacted]% in Year 1 increasing to [redacted]% in Year 6.	The uptake rate was based on the uptake of ranibizumab in its first five full years of listing (2008-2012), adjusted to account for differences in annual injection rates. This rate may be affected by changes in the population in the past 15 years. DUSC considered that the uptake rate was uncertain. DUSC noted that ranibizumab uptake was likely higher as it provided vision improvement. As the target population effectively has only-eye status, more caution in treatment uptake is expected.
Grandfathered patients	No grandfathered patients were explicitly included in the model	The submission indicated that grandfathered patients have been included in the prevalent population and are not modelled as a distinct population. This may result in an overestimate of the financial impacts as grandfathered patients receive a shorter duration of treatment.
Dose per course of treatment	4.71 injections per year, calculated from the totals at 24 months for the OAK and DERBY trials and adjusted for compliance (95.5%) to derive 4.5 injections per year.	The annual doses were held constant over the 6 years and discontinuation was applied to the patient numbers. This is consistent with the dose per course of treatment in the economic evaluation; however, this may be underestimated as described in paragraph 6.49.
Offsets	No offsets were applied to the model.	As there is currently no treatment for GA, this approach is appropriate.
Pegcetacoplan	$[redacted] (published) $[redacted] (effective)	Correctly calculated DPMQs from the provided AEMPs.
Affected MBS items		
OCT	MBS item 11219 $45.50 ($46.60) 2 services at initiation 3 services per year during treatment	This was the appropriate MBS item. The item cost was subject to annual indexation after the submission was provided. DUSC noted that OCT was limited to once every 12 months but was modelled more frequently for both initiation (2 services) and monitoring (3 services) in the financial model.
IVT injection	MBS item 42738 $342.65 (*$350.85*) 1 service per administration (4.5 per year)	This item was removed the MBS schedule from 1 July 2025. Advice from the Department indicated that MBS item 43030 and 43032 are the most appropriate alternatives. The item cost was subject to annual indexation after the submission was provided.

Source: Table 139 – Table 144, pp231-233 of the submission.

6.58 The estimated use and financial impacts of listing pegcetacoplan are shown in Table 16.

Table 16: Estimated use and financial impact of listing pegcetacoplan (effective)

Scripts						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Pegcetacoplan 15mg/0.1ml	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]
Net financial impact of pegcetacoplan						
PBS/RPBS less copayments	$[redacted][6]	$[redacted][7]	$[redacted][8]	$[redacted][9]	$[redacted][10]	$[redacted][10]
Net financial impact of affected medicines						
PBS/RPBS less copayments	$0	$0	$0	$0	$0	$0
Net financial impact						
Net PBS/RPBS	$[redacted][6]	$[redacted][7]	$[redacted][8]	$[redacted][8]	$[redacted][10]	$[redacted][10]
MBS impact	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][11]	$[redacted][11]	$[redacted][11]
Net financial impact	**$**[redacted][6]	**$**[redacted][7]	**$**[redacted][9]	**$**[redacted][10]	**$**[redacted][12]	**$**[redacted][12]

Source: The financial estimates from the submission: 3a. Scripts – proposed, 3c. Impact - proposed (eff), 4c. Impact - affected (eff), 5. Impact - net, 7. Net changes – MBS

The redacted values correspond to the following ranges:

[1] *5,000 to < 10,000*
[2] *10,000 to < 20,000*
[3] *20,000 to < 30,000*
[4] *30,000 to < 40,000*
[5] *40,000 to < 50,000*
[6] *$0 to < $10 million*
[7] *$20 million to < $30 million*
[8] *$30 million to < $40 million*
[9] *$40 million to < $50 million*
[10] *$50 million to < $60 million*
[11] *$10 million to < $20 million*
[12] *$70 million to < $80 million*

6.59 The total cost to the PBS/RPBS of listing pegcetacoplan was estimated to be $50 million to < $60 million in Year 6, and a total of $200 million to < $300 million in the first 6 years of listing.

6.60 The DUSC considered the main issues with the estimates were:

- that there was a near market comparator - avacincaptad pegol - which may influence the utilisation of pegcetacoplan.
- that the use of scripts as a basis for the modelling was reasonable but could increase the risk of errors in the estimates of later year utilisation. DUSC considered that the utilisation could have been more accurately modelled on patient numbers rather than scripts. DUSC noted that the number of scripts for 60-day dosing would come out to 6 per year. DUSC noted that the use of scripts was based only on patients who remained in the clinical trials and did not include those that discontinued.

- that the uptake could be greater with improvements in models of care. DUSC considered that there may be "warehoused" patients specifically waiting for this drug to become available on the PBS. Additionally, as there are no Grandfathered patients explicitly included in the estimates, and there is uncertainty as to whether or not all patients [redacted] will meet the proposed restriction, an initial spike in use above that estimated is considered a possibility.
- DUSC noted that there was no explicit stopping rule and that some patients may be on treatment for a prolonged duration. The pre-PBAC response argued that it is unlikely that pegcetacoplan would be used longer than expected as the proposed PBS continuation criterion requires the treated eye to have an intact fovea.

Quality Use of Medicines

6.61 The sponsor is conducting a long-term extension study to evaluate the long-term efficacy and safety of pegcetacoplan. The data through months 24 were presented in the submission, and the results (through month 36) are expected in November 2025. The sponsor is also conducting an observational phase 4 study to evaluate real-world safety, tolerability, and treatment patterns of pegcetacoplan.

6.62 The sponsor has a pharmacovigilance system in place for the Apellis Australia affiliate that work together EU and Global (based in the US) Pharmacovigilance teams.

6.63 DUSC noted that there was a risk of increased rate of nAMD, retinal vasculitis, and intraocular inflammation. This was considered manageable, but no QUM activities are proposed.

Financial Management – Risk Sharing Arrangements

6.64 The submission did not request a risk share arrangement

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the listing of pegcetacoplan, on the basis that it should be available as a General Schedule listing for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The Committee acknowledged the high clinical need for treatments for GA, which is a leading cause of irreversible vision loss in older Australians. The PBAC is satisfied that pegcetacoplan provides, for some patients, a significant improvement in efficacy over best supportive care (BSC) in slowing the growth of GA lesions. Despite no significant differences demonstrated for functional outcomes in the key trials, the PBAC considered it was reasonable to assume anatomical preservation, as evidenced by microperimetry outcomes, will result in better functional vision. As such, the PBAC accepted the economic model could be used to determine cost-effectiveness. The PBAC considered more conservative assumptions for the model would help address the uncertainty of

transforming microperimetry outcomes to best-corrected visual acuity (BCVA). The PBAC considered the cost-effectiveness analysis would be more reliable with these alternative parameters and an incremental cost-effectiveness ratio (ICER) in the order of $55,000 to < $75,000 per QALY gained would be acceptable. A price reduction would be required to achieve cost-effectiveness based on the revised model. In addition, the PBAC considered a risk sharing arrangement was needed to address any residual uncertainty regarding estimated patient numbers and to ensure PBS reimbursement was for treatment in one eye only.

7.2 The PBAC noted the support from health care professional, organisations and individuals for the PBS listing of pegcetacoplan, to provide an affordable, effective treatment to slow the progression of the disease which will impact different aspects of quality of life, including independent living, physical mobility and mental health.

7.3 The PBAC noted the high clinical need for treatments to prevent vision loss in patients with GA secondary to AMD. The PBAC noted the proposed population, who had already experienced vision loss in one eye, were the highest priority patients and agreed with the Advisory Committee on Medicines (ACM) that that this was appropriate as these patients would be motivated to accept higher risks and less certainty in outcomes in order to potentially prevent or delay the same outcome for their other eye.

7.4 The PBAC agreed with the ESC that the clinical criteria proposed for the initial and continuing treatment restrictions were clinically sound and the maximum quantity and repeats as proposed were appropriate for treatment of one dose of pegcetacoplan every other month.

7.5 The PBAC advised that the request for a grandfathering restriction for patients [redacted] would not be required as patients that would not meet the proposed PBS restriction eligibility criteria should not be eligible for PBS subsidy for pegcetacoplan (this would potentially have included patients with intact fovea in the untreated eye).

7.6 The PBAC advised that it was unlikely that pegcetacoplan would be used longer than expected, as the proposed PBS continuation criterion requires the treated eye to have an intact fovea and this would be assessed regularly.

7.7 The PBAC noted that in clinical practice, as intra-ocular inflammation most commonly occurs after the first dose of pegcetacoplan, some clinicians and patients may wish to test the safety of the drug in the worst eye (i.e. the eye that does not have an intact fovea) before proceeding to treat the other eye. The PBAC noted this was not part of the submission or proposed restriction and did not expect this dose to be PBS-subsidised, hence no increase in maximum quantities or repeats would be required for this.

7.8 The PBAC accepted the nominated comparator of BSC was appropriate. The PBAC noted from the sponsor hearing (paragraph 6.1) that therapy for concomitant or

developing neovascular (or wet) AMD would receive priority and would not be used in combination with pegcetacoplan.

7.9 The PBAC noted the submission was based on 2 phase 3 randomised controlled trials (RCTs) comparing pegcetacoplan intravitreal (IVT) monthly (PM) or every other month (PEOM) to sham injection monthly or every other month: DERBY (n=621) and OAKS (n=637). This was supplemented by two other studies: FILLY (n=246), a phase 2 RCT comparing PM or PEOM with sham injections and GALE (n=780), an ongoing, open label, long-term extension study to DERBY and OAKS. The PBAC noted the results of the OAKs trial showed a statistically significant difference in the change from baseline in total area of GA lesion at 12 months in both the PM and PEOM groups compared to sham (difference in least squares [LS] mean: PM -0.41, 95% confidence interval [CI] -0.64, -0.18; PEOM: -0.32, 95% CI: -0.54, -0.09). The PBAC accepted that, when adjusted for imbalances in baseline characteristics, the DERBY trial also reported a statistically significant difference in both the PM and PEOM groups compared to sham for this outcome (difference in LS mean: PM -0.31, 95%CI: -0.54, -0.087; PEOM: -0.29, 95% CI: -0.51, -0.07). The PBAC agreed with the ESC that the results of the GALE study indicated a continued treatment effect on GA lesions out to 48 months, although this was not comparative data.

7.10 The PBAC noted that the approved TGA product information only includes pegcetacoplan dosed every other month and considered the PEOM results most relevant to the proposed PBS population. The PBAC also noted that the whole trials populations of the DERBY and OAKS trials do not align with the requested PBS population as the whole trial populations included patients with subfoveal and non-subfoveal GA lesions at base line. The PBAC noted that pooled data from the DERBY and OAKs trial for PEOM in patients with non-subfoveal GA lesions at baseline for the outcome of change from baseline in GA lesion size reported a relative difference of −1.11 mm^2 (95% CI: −1.66, −0.57). The PBAC considered that these data demonstrated that pegcetacoplan dosed every other month in patients with non-subfoveal GA lesions at baseline slowed the growth of the GA lesions.

7.11 The PBAC noted that a statistically significant difference was not observed between the pegcetacoplan arms and the sham arms of the DERBY and OAKS trials in the secondary, functional outcomes of normal luminance BCVA, monocular maximum reading speed, functional reading independence (FRI) score, or National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25). As such, the PBAC agreed with the ESC that there was considerable uncertainty in the extent to which slowing of the progression of GA lesion growth by pegcetacoplan would translate into a delay in loss of usable vision required for independent activities of daily living.

7.12 The PBAC noted the submission argued that microperimetry outcomes were an appropriate functional measure in GA. Using microperimetry, treatment with pegcetacoplan every other month in the OAKS trial resulted in a statistically significant hazard reduction in patients experiencing a loss of both the central 4 points (hazard ratio [HR]: 0.64, 95% CI: 0.44, 0.92) and the central 16 points (HR: 0.52. 95% CI: 0.32,

0.85) when compared to sham treated patients. Despite no significant differences demonstrated for functional outcomes in the key trials, the PBAC considered it was biologically and clinically plausible to assume anatomical preservation, as evidenced by microperimetry outcomes, would delay functional vision loss. The PBAC was also reassured by the sponsor hearing that this interpretation was reasonable (paragraph 6.1). Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable but the magnitude of the effect on delaying vision loss was uncertain.

7.13 The PBAC considered the evidence presented indicated that the safety of pegcetacoplan is inferior to sham with a higher rate of adverse events related to treatment (12.1% vs. 3.9% in DERBY), higher rates of intraocular inflammation (2.7% vs. 0% in DERBY) and a higher rate of neovascular age related macular degeneration (nAMD) (7.5% vs. 2.4% in DERBY). The PBAC considered that a claim of inferior comparative safety was reasonable.

7.14 The PBAC noted the submission presented a modelled economic evaluation based on the DERBY and OAKS trials. The economic analysis modelled differences in BCVA (measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters) by assuming loss of scotomatous points detected via microperimetry can be a predictor of BCVA loss. Accordingly, the pegcetacoplan treatment effect identified in terms of a risk reduction in time to 'central 16 scotomatous points' was translated to a treatment effect in terms of BCVA. The PBAC acknowledged the concerns raised by the ESC and evaluation with the quantification of the surrogate-functional outcome relationship and the estimated treatment effect (see paragraphs 6.42 and 6.46). As outlined in paragraph 7.13, the PBAC considered it was reasonable to assume anatomical preservation based on microperimetry outcomes would result in better functional vision. As such, the PBAC considered the economic model could be used to determine cost-effectiveness with revised inputs. The PBAC considered more conservative assumptions for the model would be required to address the uncertainty of transforming microperimetry outcomes to BCVA.

7.15 The PBAC agreed with the ESC that, while the GALE extension study provided some support for the ongoing treatment effect of pegcetacoplan, a 20-year time horizon was not reasonable in this patient population. The PBAC considered a 15-year time horizon would be more appropriate. The PBAC noted the model assumed the pegcetacoplan treatment effect increased at the end of the observed trial period and continued without waning while patients remained on treatment. Acknowledging concerns regarding magnitude of effect, the PBAC advised that the treatment effect should remain the same at the end of the observed period rather than increase. The PBAC also considered the assumption of identical utilities across the two treatment arms was not appropriate given the higher rate of adverse events of pegcetacoplan administration over BSC. The PBAC advised that a utility decrement due to pegcetacoplan administration should be included. The PBAC also advised that the approach taken by the evaluation to estimating the number of pegcetacoplan injections per year based on treatment compliance reported in the trials should be

used in the economic model (see paragraph 6.49). The PBAC noted inclusion of aged care related costs in the economic model and agreed with the ESC that they included both aspects of health and non-health care which were hard to separate in the model. As such, the PBAC advised that Home Care Packages and Commonwealth Home Support Program costs should be reduced by 50% in the model as a way to address this uncertainty. The PBAC considered with these alternative parameters the cost-effectiveness analysis would be more reliable and an ICER in the order of $55,000 to < $75,000 per QALY gained would be acceptable. The PBAC noted that a price reduction would be required to achieve cost effectiveness.

7.16 The PBAC noted the DUSC advice on the financial estimates. The PBAC agreed with the DUSC that the number of pegcetacoplan scripts per year was underestimated. The PBAC advised that the number of pegcetacoplan scripts per year should be revised to reflect treatment compliance reported in the key trials (i.e. 5.39 scripts per year). The PBAC noted the submission assumed a [redacted]% and [redacted]% uptake rates in Year 1 and Year 2 respectively. The PBAC agreed with the DUSC that the uptake rates were uncertain with the possibility of some hesitation due to the effective "one-eye" status of the target population. However, the PBAC noted that there are no other subsidised treatment options available for GA and that in clinical practice some clinicians may test the safety of pegcetacoplan in the worst eye first (see paragraph 7.6). As such, the PBAC advised that the uptake rate in both Year 1 and Year 2 be increased to [redacted]% with the uptake rates in the remaining years as per the submission. The PBAC considered that, with these amendments and with the price reduction required to achieve cost effectiveness outlined in paragraph 7.15, it would be reasonable to accept the financial estimates as the basis of a risk sharing arrangement.

7.17 The PBAC considered that a risk sharing arrangement was required to address any residual uncertainty regarding estimated patient numbers and to ensure PBS reimbursement was for treatment in one eye only. The PBAC recommended an [redacted]% rebate for treatment costs above the annual caps amended as per paragraph 7.16.

7.18 The PBAC advised that pegcetacoplan is not suitable for prescribing by nurse practitioners. The PBAC also recommended that pegcetacoplan is suitable for prescribing by an ophthalmologist or by an accredited ophthalmology registrar, in consultation with an ophthalmologist only. GA secondary to AMD should be diagnosed using fundus autofluorescence or optical coherence tomography (OCT) with ongoing assessment to ensure that the fovea remains intact.

7.19 The PBAC recommended that the Early Supply Rule should not apply.

7.20 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for pegcetacoplan:

a) The treatment is expected to provide a clinically relevant improvement in efficacy over

standard care for slower GA lesion growth and slower reduction in microperimetry outcomes, however, the magnitude of the effect on delaying vision loss was uncertain.

b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no other drugs listed on the PBS for this population.

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.21 The PBAC advised that this submission would not be eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
PEGCETACOPLAN					
pegcetacoplan, 15 mg/0.1 mL injection, 0.1 mL vial	NEW	1	1	2	Syfovre
Restriction Summary [new1] / Treatment of Concept: [new1A]					
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (FULL assessment) in writing only via OPA/post/HPOS upload				
Prescribing rule level	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Episodicity:				
	Severity:				
	Condition: Geographic Atrophy (GA)				
	Indication: Geographic Atrophy (GA)				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	The condition must be secondary to age-related macular degeneration (AMD)				
	AND				
	Clinical criteria:				
	The condition must be diagnosed by optical coherence tomography;				
	OR				
	The condition must be diagnosed by fundus autofluorescence				

	AND
	Clinical criteria:
	The patient must have non-subfoveal geographic atrophy (GA) lesion(s), distanced from the centre point of the fovea by at least 1 micrometre in the treated eye
	AND
	Clinical criteria:
	Patient must have subfoveal GA lesion(s) involving the foveal centre point in the non-treated eye causing vision impairment (i.e. the fovea is no longer intact)
	AND
	Clinical criteria:
	Patient must have central vision in the treated eye threatened by growth of GA lesion(s), defined as either: (i) located within the 750 micrometre radius of the foveal centre, or (ii) located beyond 750 micrometres from the foveal centre, where historical imaging shows lesion progression toward the foveal centre, and is located within the macula (defined as the 5.5 millimetre diameter area).
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist.
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System (see www.servicesaustralia.gov.au/hpos) or in writing via HPOS form upload or mail and must include: (1) Details (date, unique identifying number/code or provider number) of the optical coherence tomography or fundus autofluorescence report.
	If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). All reports must be documented in the patient's medical records.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
PEGCETACOPLAN					
pegcetacoplan, 15 mg/0.1 mL injection, 0.1 mL vial	NEW	1	1	2	Syfovre

Restriction Summary [new2] / Treatment of Concept: [new2A]		
Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (Streamlined) [NEW]
Prescribing rule level		**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Episodicity:
		Severity:
		Condition: Geographic Atrophy (GA)
		Indication: Geographic Atrophy (GA)
		Treatment Phase: Continuing treatment
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye
		AND
		Clinical criteria:
		The condition must be secondary to age-related macular degeneration (AMD).
		~~**AND**~~
		AND
		Clinical criteria:
		The treatment must be the sole PBS-subsidised therapy for this condition
		AND
		Clinical criteria:
		The patient must have non-subfoveal GA lesion(s), distanced from the centre point of the fovea by at least 1 micrometre in the treated eye
		Treatment criteria:
		Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist.
		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the

merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.