5.02 AVACINCAPTAD PEGOL, Solution for intravitreal injection, 2 mg in 0.1 mL (20 mg per mL), Izervay®, Astellas Pharma Australia Pty Ltd

1 Purpose of submission

1.1 The Category 1 submission requested a General PBS/RPBS listing of avacincaptad pegol (ACP) for the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) who have an intact fovea and where central vision is threatened by GA lesion growth.

1.2 Listing was requested on the basis of a cost-utility analysis 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	Adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) with an intact fovea and when central vision is threatened by GA lesion growth.
Intervention	Avacincaptad pegol (ACP; IZERVAY®) 2mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately 28 ± 7 days) for up to 12 months.
Comparator	Clinical comparator: Best supportive care — In GATHER1 and GATHER2 trials, represented by sham/placebo Near-market comparator: Pegcetacoplan (Syfovre®), clinical comparison only
Outcomes	Mean change in GA area from baseline (using square root transformation), over 12 months (GATHER 1) Mean rate of GA growth (slope) from baseline (using square root transformation), over 12 months (GATHER2) Mean change in best-corrected visual acuity (BCVA) from Baseline to Month 12 Mean change in low-luminance (LL) BCVA from Baseline to Month 12 Safety: Treatment- emergent adverse events (TEAEs)
Clinical claim	ACP is superior in terms of efficacy and is inferior in terms of safety compared to best supportive care (sham/placebo in clinical trials). ACP is non-inferior to pegcetacoplan in terms of clinical effectiveness and safety.

Source: Table 1.1-1, p25 of the submission.
ACP = avacincaptad pegol; AMD = age-related macular degeneration; BCVA = Best corrected visual acuity; GA = geographic atrophy; mg = Milligram.

2 Background

Registration status

2.1 ACP received Therapeutic Goods Administration (TGA) registration on 13 October 2025 for the treatment of adult patients with GA secondary to AMD who have an intact fovea and where central vision is threatened by GA lesion growth. This was the first registration of ACP on the Australian Register of Therapeutic Goods (ARTG).

Previous PBAC consideration

2.2 The PBAC has not previously considered ACP for the treatment of GA secondary to AMD. The PBAC has previously considered pegcetacoplan, which was recommended for the treatment of GA secondary to AMD in November 2025.

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

3 Requested listing

3.1 An abridged version of the proposed restrictions is provided below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Avacincaptad pegol (IZERVAY®)					
Avacincaptad pegol intravitreal solution, 2 mg/0.1 mL in a single-dose vial	Published: $[redacted] Effective: $[redacted]	1	1	5	IZERVAY® Astellas Pharma Australia Pty. Ltd.

mg = Milligram; Rpts = repeats.

Category / Program: General Schedule (Code GE)
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)
Indication: Geographic atrophy (GA) secondary to age-related macular degeneration (AMD).
Treatment Phase: Initial
Clinical criteria: Patients must have an intact fovea AND For the treatment of a single eye where a patient's central vision is threatened by GA lesion growth AND Patient must have non-sub-foveal geographic atrophy secondary to age-related macular degeneration AND The condition must be diagnosed by fundus autofluorescence (FAF) or optical coherence tomography (OCT) AND The treatment must be the sole PBS-subsidised therapy for this condition
Treatment criteria: Must be treated by an ophthalmologist experienced in the management of geographic atrophy and in administering intravitreal injections.

Population criteria: Patient must be adult
Prescribing Instructions: The vial is for single use in one eye only. Discard any residue.
Administrative Advice: Note Special Pricing Arrangements apply. 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.

AMD = age-related macular degeneration; anti-VEGF = anti-vascular endothelial growth factor; GA = geographic atrophy; IOP = Intraocular pressure; OCT = optical coherence tomography; OR = Odds ratio; PBS = Pharmaceutical Benefits Scheme; VEGF = vascular endothelial growth factor.

Category / Program: General Schedule (Code GE)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (Streamlined)
Indication: Geographic atrophy (GA) secondary to age-related macular degeneration (AMD).
Treatment Phase: Continuing
Clinical criteria: The condition must be due to geographic atrophy secondary to age-related macular degeneration AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have previously received PBS-subsidised treatment with this drug for this condition for the same eye AND Patient must have demonstrated continued clinical benefit of the condition, the details of which must be kept with the patient's record OR Patient must not continue treatment with avacincaptad pegol until endophthalmitis, retinal detachment or intraocular inflammation if developed, have resolved. OR If patient develops neovascular (wet) AMD or choroidal neovascularisation develops, treatment with an appropriate anti-Vascular Endothelial Growth Factor (anti-VEGF) agent should be considered.
Treatment criteria: Must be treated by an ophthalmologist experienced in the management of geographic atrophy and in administering intravitreal injections.
Population criteria: Patient must be adult
Prescribing Instructions: The vial is for single use in one eye only. Discard any residue.
Administrative Advice: Note Special Pricing Arrangements apply.

AMD = age-related macular degeneration; anti-VEGF = anti-vascular endothelial growth factor; GA = geographic atrophy; IOP = Intraocular pressure; OCT = optical coherence tomography; OR = Odds ratio; PBS = Pharmaceutical Benefits Scheme; VEGF = vascular endothelial growth factor.

3.2 The submission requested a special pricing arrangement (SPA). The requested published ex-manufacturer price (EMP) is $[redacted] per vial and the effective EMP is $[redacted] per vial.

3.3 The submission stated that the eligibility criteria for initiation of ACP treatment were consistent with the approved ACP Product Information (PI) and the key clinical trials and did not include patients with sub-foveal GA lesions. The clinical criteria of the proposed PBS restriction for initial ACP treatment aligned with the approved ACP PI.

However, the proposed restriction for initiation of ACP treatment did not align with the patient eligibility criteria used in the key trials, in several ways:

- The key trials did not include patients with diagnosed choroidal neovascularisation (CNV) or other ocular conditions that can progress during ACP treatment. However, co-existence of the two conditions is not uncommon (7.4%/patient-year for symptomatic CNV in GA patients and macular atrophy subsequent to CNV in 24–37% of GA patients over 2 years)[1], and these patients were included in the proposed treated population. There will be applicability issues when applying the trial results to the proposed benefits in the treated population in the Australian setting. The Pre-Sub-Committee Response (PSCR) noted that patients with suspected CNV were withdrawn from GATHER1, while in GATHER2, patients who developed CNV were permitted to receive concomitant anti-vascular endothelial growth factor (anti-VEGF) therapy. CNV was also reported as a treatment emergent event in the GATHER1 and GATHER2 trials with the PSCR noting that patients who developed CNV were older at baseline than those who did not. The PSCR stated that data from the IRIS Registry showed that 34.3% of patients had CNV or neovascular AMD at baseline prior to treatment initiation. During follow-up 22.7% of treated eyes received concomitant anti-VEGF therapy, of these, approximately 90% had prior exposure to anti-VEGF treatment. The ESC considered that balancing the risk of progressive CNV with treatment for GA will be a key consideration by the treating specialist. It will select out a proportion of these patients where the risk of progressing CNV with this treatment will outweigh the potential benefits of treatment.
- The proposed restriction does not define the distance between the GA lesion and the foveal centre. This could result in a wider population being eligible for ACP treatment — as patients with their GA lesions further away from the foveal centre are at lower risk of progression and therefore may not need treatment. The proposed restriction also does not define the size of the GA area eligible for treatment. A wider population may therefore be eligible for treatment than is necessary — some GA patients may have GA lesions that are too small to threaten their central vision, some patients' GA lesions may already be too large in size and loss of central vision is inevitable despite treatment (ACP cannot reverse atrophy, only slow progression). The PSCR stated that accurate measurements require specialist imaging and argued that in real-world practice the reliability of micrometre or area-based cut-offs may be reduced. The PSCR also argued that the intent of the trial criteria was to identify patients at risk of central vision loss rather than to establish absolute numeric thresholds for treatment eligibility. The ESC considered that diagnostic methods such as optical coherence tomography (OCT) and fundus autofluorescence (FAF) are widely used in Australia by

[1] Keiko K, Gale R, Li X et al. Simultaneous GA and CNV/MNV: incidence, characteristics, and treatments. *Graefes Arch Clin Exp Ophthalmol* 2025.14;263(5): 1197-1212.

ophthalmologists for detecting and monitoring GA. The ESC noted that the key consideration is the risk to central vision as this is an important factor in this elderly group of patients which may result in the person going from independent to dependent in activities of daily living. The ESC advised that it would be appropriate to specify in the restriction if the lesion was located within a specific radius from the foveal centre, or if outside of that radius, the GA lesion is within the macula and historical imaging indicates progression towards the foveal centre. The pre-PBAC response argued incorporating fixed distance thresholds or prescriptive historical imaging requirements would risk excluding patients who could clinically benefit, create administrative burden without improving patient selection, and reduce alignment with routine ophthalmic practice. It was suggested in the pre-PBAC response that appropriate targeting can instead be achieved by restricting treatment to patients with GA secondary to AMD who have an anatomically intact fovea. It was claimed that a clinician-based definition of central vision threat, based on specialist assessment with standard imaging as opposed to fixed distance criteria required by a PBS restriction, would be preferable.

3.4 For patients who are receiving continuing ACP treatment but develop CNV, it was stated in the proposed restriction that treatment with an appropriate anti-vascular endothelial growth factor (anti-VEGF) agent should be considered, and the decision whether to continue ACP should be made by the treating ophthalmologist based on clinical judgment. This is consistent with the approved ACP PI. Compared to the dry (atrophic) AMD, neovascular changes are more rapid and are frequently more sight-threatening. Based on the Advisory Committee on Medicines (ACM)'s comment, if a patient is under ACP treatment for GA but develops CNV, it is mostly likely that the treating ophthalmologist will suspend the ACP therapy and prioritise treating CNV.

3.5 The proposed restriction included a criterion stating that ACP is 'For the treatment of a single eye where a patient's central vision is threatened by GA lesion growth'. Consistent with the GATHER1 and GATHER2 trials the restriction states that use is for treatment of a single eye. However, no further detail is provided as to what would occur if both eyes were to present with the condition. When asked to comment on the overall benefit-risk balance of ACP, the ACM stated that 'it was important that the decision to use ACP is based on informed consent, and that for a small number of patients, the benefits of possible maintenance of visual acuity may have an impact on independence and functioning, especially for those with monocular vision'. The PSCR stated it did not consider it necessary to further specify vision status in the non-treated eye or to restrict use to one eye per lifetime, as such requirements were not evaluated in the clinical trials and may unduly limit clinically appropriate use in a progressive condition. The ESC noted the ACM advice that the benefits may be higher in those with monocular vision. In addition, the ESC noted that pegcetacoplan requested listing for the treatment of GA secondary to AMD where the treated eye has an intact fovea and the non-treated eye does not have an intact fovea and was recommended for use in one eye only (pegcetacoplan PBAC Meeting Outcomes, November 2025 PBAC

meeting). The ESC considered that it would be appropriate to restrict use to one eye only in patients with monocular vision consistent with the proposed pegcetacoplan restriction.

3.6 The submission did not propose a separate restriction for grandfathering treatment. In the submission, it was stated that there will be < 500 patients with GA secondary to AMD who are accessing ACP privately, and the PBS restriction for continuing treatment would allow grandfathered patients to access ACP. However, the continuing restriction would require patients to have previously received PBS-subsidised treatment with this drug. The PSCR provided a draft grandfathering restriction. The ESC noted that the draft included clinical criteria which required patients to have previously received PBS-subsidised treatment and advised that this requirement was not appropriate for a grandfathering restriction. The ESC considered that additional changes would also be required based on the advice provided by the Committee on the initial and continuing restrictions.

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

4 Population and disease

4.1 GA occurs during the advanced stage of the non-neovascular form of AMD (dry AMD) which is a leading cause of irreversible vision loss in older adults[2]. AMD is a progressive degenerative disease of the macula (central retina) and results in impairment of central vision[3]. The fovea is the central part of macula and is densely populated with photoreceptors, critical for the visual acuity required for daily tasks such as reading, driving, and recognising faces[3].

4.2 GA is characterised by well-demarcated areas of retinal atrophy involving the retinal pigment epithelium (RPE), photoreceptors, and underlying choriocapillaris. GA is a progressive disease and typically begins in the perifoveal area. Its progression leads to irreversible central blindness over time, and the median time to legal blindness is estimated at 6.2 years[4]. In patients with GA, peripheral vision is spared. However, the loss of central vision significantly affects quality of life[5]. Major risk factors of GA include advanced age, family history, and smoking. The burden of GA is an increasing public health issue in aging populations including in Australia[6].

[2] Fleckenstein M, Mitchell P, Freund KB, Sadda S, Holz FG, Brittain C, et al. The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. *Ophthalmology*. 2018;25(3):369-90.
[3] Flores R, Carneiro Â, Vieira M, Tenreiro S, Seabra MC. Age-Related Macular Degeneration: Pathophysiology, Management, and Future Perspectives. *Ophthalmologica*. 2021;244(6):495-511.
[4] Geographic atrophy (GA). Retina Australia. URL: https://retinaaustralia.com.au/
[5] Krogh Nielsen M, Hinnerskov JMV, Sørensen TL. Geographic atrophy: Signs, symptoms, and quality of life. *Acta Ophthalmologica*. 2023; 101(8):896-902.
[6] Macular Disease Foundation Australia. Navigating the changing geographic atrophy landscape. URL: https://www.mdfoundation.com.au/wp-content/uploads/2024/08/13283-MDFA-New-HCP-Training-Manual-A4x24PP.pdf

4.3 The Australian National Eye Health Survey in 2017 revealed that bilateral AMD occurred in 42.6% of surveyed subjects[7]. In eyes with nonfoveal GA, the 4-year risk of foveal involvement was 57%[8]. In half of the GA cases, the condition progressed to both eyes within 7 years of initial diagnosis[9].

4.4 The complement cascade, particularly the alternative pathway involving components such as C3 and C5, has been implicated in the growth of GA and RPE degeneration[10]. Currently, pegcetacoplan (a C3 inhibitor) and ACP (a C5 inhibitor) are approved by the TGA for GA secondary to AMD. ACP is approved for once monthly intravitreal (IVT) injection (single eye) for the first 12 months, with a dosage of 2 mg (0.1 mL of 20 mg/mL solution) followed by once monthly or every other month thereafter.

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 monitoring for disease progression and development of neovascular AMD (nAMD), lifestyle management, optimising spectacles, and referral to low vision services. The main argument provided in support of this nomination was that, at the time when the submission was prepared, there were no therapies for GA listed on the PBS. The ESC considered the nominated comparator was appropriate.

5.2 The submission also nominated pegcetacoplan as a near market comparator. Pegcetacoplan is TGA approved for adult patients with GA secondary to age related AMD with an intact fovea and when central vision is threatened by GA lesion growth. Pegcetacoplan is TGA approved for IVT injection (single eye) once every other month with the dosage of 15 mg (0.1 mL of 150 mg/mL solution) and was recently recommended by PBAC for PBS listing (Pegcetacoplan, November 2025 PBAC Meeting outcomes).

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

[7] Keel S, Xie J, Foreman J, van Wijingaarden P, Taylor HR, Dirani M. Prevalence of age-related macular degeneration in Australia: The Australian National Eye Health Survey. *JAMA Ophthalmology.* 2017; 135(11): 1242-1249.

[8] Keenan TD, Agrón E, Domalpally A, Clemons TE, van Asten F, Wong WT et al. Progression of geographic atrophy in age-related macular degeneration: AREDS2 Report Number 16. *Ophthalmology*. 2018; 125 (12): 1913-1928.

[9] Lindblad AS, Lloyd PC, Clemons TE, Gensler GR, Ferris FL, Klein ML et al. Ghance in area of geographic atrophy in the Age-related Eye Disease Study: AREDS Report number 26. *Archives of Ophthalmological Research.* 2009; 127 (9): 1168-1174.

[10] Wilke GA, Apte RS. Complement regulation in the eye: Implications for age-related macular degeneration. *Journal of Clinical Investigation*. 2024; 134(9). Accession Number: 38690727 PMCID: PMC11060743 DOI: 10.1172/jci178296.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (14), health care professionals (5) and a consumer group (1) via the Office of Health Technology Assessment Consultation Hub. The PBAC acknowledged that the individuals who would like access to ACP for themselves, or their family, described how declining eyesight leads to a loss of independence, and affects one's ability to read, drive, work, care for others and engage in community life. Several inputs expressed fear of future blindness and the psychological burden it creates. Input conveyed strong hope that ACP could slow the progress of GA and even potentially improve eyesight. The PBAC noted treatment with ACP would not improve eyesight but may potentially delay vision loss. Even a modest slowing of decline was considered by individuals to meaningfully protect independence and potentially reduce the need for greater public support in later stages. Cost was consistently identified as the dominant barrier to access, with many individuals indicating that, without subsidised access, they will be unable to receive treatment.

6.3 The PBAC noted input from an individual that reflected lived experiences with a condition that was not GA secondary to AMD. The input suggested emerging medications like ACP could also potentially benefit other retinal conditions. The PBAC advised that input from consumers is most useful when it relates directly to the indication being considered but acknowledged the value of broader perspectives in understanding community experiences with medicines.

6.4 The PBAC noted mixed support from health care professionals, with some noting delayed retinal degeneration would offer meaningful benefit by helping patients retain their sight for longer, with others suggesting the evidentiary basis for PBS listing was limited and such mild/small delays in anatomical progression of GA were insufficient to translate into meaningful outcomes for patients.

6.5 The PBAC noted the advice received from Macular Disease Foundation Australia which highlighted the effects of vision loss on everyday living from the global Geographic Atrophy Insights Survey (GAINS), which included Australian respondents aged 60 years and older with self-reported geographic atrophy in one or both eyes. The survey found that vision loss resulted in respondents experiencing moderate or major negative impacts on their ability to drive (73%-75%), read (66%-71%) and travel (62%). Respondents also reported moderate or major negative impacts on their self-confidence (49%-56%), and moderate or major negative impacts on their mental health (40%).

Clinical trials

6.6 The submission was based on two ACP trials: GATHER1 (Phase 2/3) and GATHER2 (Phase 3). Both trials were randomised, double-masked, Sham-controlled trials. GATHER1 (N = 286) had a treatment period of 18 months and GATHER2 (N = 448) had a treatment period of 24 months. In Part 1 of GATHER1, patients were randomised to receive ACP 1 mg IVT, ACP 2 mg IVT, or Sham. In Part 2 of GATHER1, patients were randomised to receive ACP 2 mg IVT, ACP 4 mg IVT, or Sham. In GATHER1, there were 67 patients in the combined ACP 2 mg group (N = 67) and 110 patients in the combined Sham group (N = 110). In GATHER2, patients were randomised at baseline to receive either monthly ACP 2 mg IVT (N = 225) or Sham (N = 222). At Month 12, after the collection of data for the primary endpoint analyses, patients who had previously received monthly ACP 2 mg IVT were re-randomised to receive either ACP 2 mg monthly (EM) (N = 96) or ACP 2 mg every other month (EOM) (N =93).

6.7 Since no head-to-head trials directly compare the efficacy and safety of ACP vs pegcetacoplan in the proposed target population, the submission presented three indirect treatment comparisons (ITCs): an anchored matching-adjusted indirect comparison (MAIC)[11] (the Sham arm was an anchor), an ITC using network meta-analysis (NMA)[12], and an ITC using multi-level network meta-regression (ML-NMR)[13]. The MAIC was informed by GATHER2, and the DERBY and OAKS pegcetacoplan trials; the ML-NMR was informed by GATHER1 and GATHER2, and DERBY, OAKS, and FILLY. The NMR included ten RCTs and five complement inhibitors (ACP [C3i], pegcetacoplan [C5i], lampalizumab [Factor D], CLG561 [C3i and C5i], and LFG316 [C5i]) for analyses.

6.8 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
Avacincaptad pegol trials		
GATHER1 NCT02686658	A Phase 2/3 randomised, double-masked, controlled trial to assess the safety and efficacy of intravitreous administration of Zimura™ (anti-C5 aptamer) in patients with geographic atrophy secondary to dry age-related macular degeneration (The GATHER1 Study).	
	Jaffe GJ et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal Phase 2/3 trial.	*Ophthalmology* 2021; 128(4):576–586.
	Patel SS et al. Avacincaptad pegol for geographic atrophy secondary to age-related macular degeneration: 18-month findings from the GATHER1 trial.	*Eye (Lond)* 2023;37(9): 1797–1805.

[11] Hahn P, Eichenbaum D, Dhoot D et al. Efficacy of intravitreal pegcetacoplan vs avacincaptad pegol in patients with geographic atrophy. *J Vitreoretin Dis* 2025. DOI 10.1177/24741264251379842

[12] Wang H, Zheng J, Zhang Q et al. Efficacy and safety of complement inhibitors in patients with geographic atrophy associated with age-related macular degeneration: a network meta-analysis of randomized controlled trials. *Front Pharmacol* 2024; 15:1410172.

[13] Jovanović J, Daki V, Kantidakis G et al. (2025) Comparative efficacy and safety of avacincaptad pegol vs pegcetacoplan in treatment of geographic atrophy: insights from a multilevel network meta-regression (Conference paper).

Trial ID	Protocol title/ Publication title	Publication citation
	Corradetti G et al. Progression to complete retinal pigment epithelium and outer retinal atrophy (cRORA): post hoc analysis of the GATHER1 trial.	*Graefes Arch Clin Exp Ophthalmol* 2025; 263(3):669–677
GATHER2 NCT04435366	A Phase 3 multicenter, randomised, double masked, sham-controlled clinical trial to assess the safety and efficacy of intravitreal administration of Zimura (complement C5 inhibitor) in patients with geographic atrophy secondary to age-related macular degeneration (The GATHER2 Study). Khanani AM et al. Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial.	*Lancet* 2023; 402:1449-58.
Pooled (GATHER1/2)	Danzig CJ et al. Vision loss reduction with avacincaptad pegol for geographic atrophy: a 12-month post hoc analysis of the GATHER1 and GATHER2 trials.	*Ophthalmol Retina* 2024;8(11):1052–1060.
Pegcetacoplan trials		
OAKS and DERBY NCT03525613; NCT03525600	Heier JS 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. Schmidt-Erfurth U et al. Disease activity and therapeutic response to pegcetacoplan for geographic atrophy identified by deep learning-based analysis of OCT. Chakravarthy U et al. Visual function benefit after treatment with pegcetacoplan: microperimetry analysis from the Phase 3 OAKS trial. Fu DJ et al. Pegcetacoplan treatment and consensus features of geographic atrophy over 24 months. Chiang A et al. Visual Acuity and Quality of Life Outcomes with Pegcetacoplan Treatment: A Post Hoc Analysis from the OAKS and DERBY Trials.	*Lancet* 2023; 401:125-37. *Ophthalmology* 2025; 132(2):181-193 *Am J Ophthalmol* 2025; 273:119–129. *JAMA Ophthalmol* 2024; 142(6):548-58. *Am J Ophthalmol* 2025; 277:471-481.
FILLY NCT02503332	Liao DS et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: A randomised phase 2 Trial. Vogl WD et al. Predicting topographic disease progression and treatment response of pegcetacoplan in geographic atrophy quantified by deep learning. Nittala MG 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. Wykoff CC et al. Characterising new onset exudation in the randomised Phase 2 FILLY trial of complement inhibitor pegcetacoplan for geographic atrophy. Steinle NC et al. Impact of baseline characteristics on geographic atrophy progression in the FILLY trial evaluating the complement C3 inhibitor pegcetacoplan. Fu DJ et al. Evaluating the effects of C3 inhibition on geographic atrophy progression from deep-learning OCT quantification: a split-person study. Fu DJ 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. Wykoff CC, Grossi F. APL-2, a complement C3 inhibitor, slows the growth of geographic atrophy secondary to AMD: 18-month results of a phase 2 trial (FILLY).	*Ophthalmology* 2020; 127(2): 186-195. *Ophthalmology Retina* 2023; 7(1): 4-13. *JAMA Ophthalmology* 2022; 140(3): 243-249. *Ophthalmology* 2021; 128(9):1325-1336. *Am J Ophthalmol* 2021; 227: 116-124. *Ophthalmol Ther* 2023; 12(6): 3143-3158. *Br J Ophthalmol* 2023; 24: bjo-2022-322672. *ARVO Annual Meet Abstract. 2018; 59(9):72.*

Trial ID	Protocol title/ Publication title	Publication citation
	Garg S et al. Impact of baseline imbalances on the efficacy of pegcetacoplan for the treatment of geographic atrophy (GA): A post hoc analysis of OAKS, DERBY, and FILLY.	*Invest Ophthalmol Vis Sci.* 2022; 63(7):1501.
GALE NCT04770545	Goldberg RA et al. Pegcetacoplan for geographic atrophy over 30 months: Data from OAKS, DERBY, and the GALE long-term extension study. Abbey AM et al. Long-term efficacy and safety of pegcetacoplan over 36 months including 12-month results of the GALE open-label extension study.	*Ophthalmic Surg Lasers Imaging Retina.* 2025; 56(7):398–406. *Invest Ophthalmol Vis Sci*. 2024; 65:380.
Observational evidence	Kailani Z et al. Ocular adverse events associated with pegcetacoplan and avacincaptad pegol for geographic atrophy: A population-based pharmacovigilance study. Rush RB, Klein W, Reinauer RM. Real-world outcomes with complement inhibitors for geographic atrophy: A comparative study of pegcetacoplan versus avacincaptad pegol. Rush RB et al. Real-world outcomes in pre-existing neovascular age-related macular degeneration subjects undergoing avacincaptad therapy for geographic atrophy. Rush RB et al. One-year outcomes in subjects developing macular neovascularization while undergoing avacincaptad pegol therapy for geographic atrophy.	*Am J Ophthalmol.* 2025; 276:252–260. *Clin Ophthalmol.* 2025; 19:1167–1174. *Clin Ophthalmol.* 2024; 18:4011–4018. *Clin Ophthalmol.* 2025; 19:111–118.
Indirect treatment comparison	Wang H et al. Efficacy and safety of complement inhibitors in patients with geographic atrophy associated with age-related macular degeneration: a network meta-analysis of randomized controlled trials. Zarbin MA et al. Pegcetacoplan vs avacincaptad pegol in geographic atrophy: an anchored matching-adjusted indirect comparison of three phase 3 trials.	*Front Pharmacol.* 2024 Nov 12; 15:1410172. *Invest Ophthalmol Vis Sci.* 2024 Jun; 65(8):6487.
	Jovanovik. Comparative efficacy and safety of avacincaptad pegol vs. pegcetacoplan in treatment of geographic atrophy: insights from a multi-level network meta-regression.	*Value in Health.* 2025; 28(S2)

Source: Table 2.2-1, pp54-57 of the submission.
AMD = age-related macular degeneration; C3 = Complement component 3; C5 = Complement component 5; GA = geographic atrophy; OCT = optical coherence tomography; RPE = Retinal pigment epithelium.

6.9 The key features of GATHER1 and GATHER2 are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
ACP vs BSC						
GATHER1	286	R, MC, DB 18 months	Low	GA secondary to AMD	Primary: mean rate of change in GA area[a] from BL Secondary: change in BCVA (ETDRS letters) from BL, change in LL-BCVA (ETDRS letters) from BL, VFQ-25 subscale score	Lesion growth and distance from fovea
GATHER2	448	R, MC, DB 24 months	Low	GA secondary to AMD	Primary: mean rate of GA growth[a] from BL Secondary: change in BCVA (ETDRS letters) from BL, change in LL-BCVA (ETDRS letters) from BL, VFQ-25 subscale score Exploratory: time to persistent vision loss from BL[b]	Lesion growth and distance from fovea (used in the scenario analysis pooled with GATHER1 data)

Source: Compiled during the evaluation; Table 2.3-2, p68; Table 2.3-3, pp70-74 of the submission.
ACP = avacincaptad pegol; AMD = age-related macular degeneration; BCVA = Best corrected visual acuity; BL = baseline; BSC = Best supportive care; DB = double blind; ETDRS = Early Treatment Diabetic Retinopathy Study; GA = geographic atrophy; LL-BCVA = Low luminance best corrected visual acuity; MC = multi-centre; R = randomised; VFQ = Visual Function Questionnaire.
[a] Square root transformed
[b] Defined as a loss of ≥ 15 ETDRS letters in BCVA from baseline measured at any 2 or more consecutive visits up to Month 24.

6.10 Both GATHER1 and GATHER2 enrolled patients aged ≥ 50 years who were diagnosed with non-subfoveal GA. In GATHER1, patients were withdrawn from the study if they developed CNV in the study eye during the course of the study, while in GATHER2, such patients remained in the study and received anti-vascular endothelial growth factor (anti-VEGF) agents for treatment of CNV.

6.11 In both trials, the number of female patients were more than double that of male patients. This differs to the Australian population. The Australian National Eye Health Survey demonstrated a slightly higher number of females with AMD compared to male (58.9% vs 41.1%)[14], probably due to the longer lifespan in females in general. While there is a discrepancy, it is unclear how this difference would impact the applicability of the trial results to the Australian population.

6.12 In both trials, the mean rate of change in GA area was the outcome used to support the clinical claim in the submission that ACP is superior in terms of effectiveness to sham/BSC. How these results can be translated into a patient-relevant outcome such as delay in loss of functional vision for patients affected by non-subfoveal GA was not demonstrated in either trial. However, based on the TGA Delegate's overview, GA area has emerged as an appropriate variable to assess progression of GA, in particular in the earlier stages of the disease, since visual acuity would poorly reflect GA

[14] Keel S, Xie J, Foreman J et al. Prevalence of age-related macular degeneration in Australia: The Australian National Eye Health Survey. *JAMA Ophthalmology* 2017; 135(11): 1242-1249.

progression if the fovea remains unaffected. In its consideration of pegcetacoplan, the PBAC noted evidence from the clinical trials showed pegcetacoplan reduced GA lesion growth by around 21% with monthly dosing and 16% with every-other-month dosing at 24 months compared to sham treatment. The PBAC considered that, although the clinical trials did not demonstrate clear improvements in vision related activities, it was reasonable to assume that protecting the structure of the eye by slowing GA lesion growth will result in slower loss of functional vision than current care. Despite uncertainty in the magnitude of this benefit on vision, the PBAC was satisfied that pegcetacoplan provides, for some patients, a significant improvement in efficacy over BSC (Pegcetacoplan, November 2025 PBAC Meeting outcomes).

6.13 OAKS and DERBY were two 24-month, phase 3, multicentre, randomised, double-masked, Sham-controlled trials comparing pegcetacoplan IVT with Sham injections in patients with GA secondary to AMD. There were 1,211 patients in the modified ITT population in OAKS and DERBY (N = 1,211). In these trials, patients were randomly assigned (2:2:1:1) to pegcetacoplan 15 mg IVT injection monthly or every other month (EOM), or to Sham monthly or EOM (stratified by GA lesion area at screening, history or presence of active choroidal neovascularisation in the fellow eye). The primary endpoint was the change from baseline to Month 12 in the total area of GA in the study eye based on fundus autofluorescence (FAF) imaging. FILLY was a phase 2, prospective, multicentre, randomised, Sham-controlled study. Patients (N = 246) were randomly assigned to (2:2:1:1) to pegcetacoplan 15 mg IVT injection monthly or EOM, or to Sham monthly or EOM. The primary efficacy end point was mean change in square root GA lesion area from baseline to Month 12.

6.14 Across the ACP trials (GATHER1 and GATHER2) and pegcetacoplan trials (OAKS and DERBY), common patient eligibility criteria included a lower limit of best corrected visual acuity (BCVA) of 20/320, GA area between 2.5 mm^2 and 17.5 mm^2, and at least one focal lesion with area ≥ 1.25 mm^2 if GA was multifocal.

6.15 Key differences in patient eligibility criteria between the ACP trials and the pegcetacoplan trials include the following:

- Fellow eye CNV at baseline was excluded in GATHER1 and GATHER2 but not excluded in OAKS and DERBY[15].
- In GATHER1 and GATHER2, only patients with non-subfoveal GA in study eyes were included, while in OAKS and DERBY, non-subfoveal and subfoveal lesions in study eyes were allowed[16].
- In GATHER1 and GATHER2, GA lesion borders entirely within 1500 µm from the foveal centre and vision between 20/25 and 20/320 were required. However, these were not required in OAKS and DERBY.

[15] In OAKS and DERBY, fellow eye CNV at baseline was identified in 45 (21%), 39 (18%), and 45 (21%) patients in OAKS, and in 39 (19%), 42 (20%), and 42 (20%) patients in DERBY who received pegcetacoplan monthly, EOM, and sham, respectively.
[16] In OAKS, 116 (57%), 131 (63%), and 147 (71%) patients, and in DERBY, 129 (63%), 120 (60%), and 122 (63%) patients who received pegcetacoplan monthly, EOM, and sham, respectively, had GA lesions in study eye involving the fovea.

Comparative effectiveness

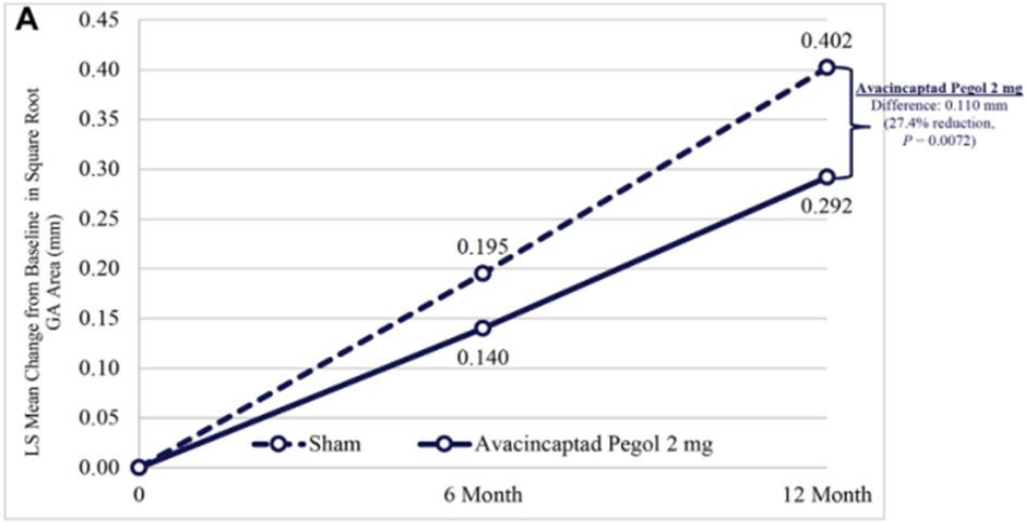
6.16 Results of the primary endpoint in GATHER1 are presented in Table 4, Figure 1, and Figure 2.

Table 4: Mean rate of change in GA area from baseline to months 12 and 18 in GATHER1 (study eye, ITT population)

	Combined ACP 2mg (N=67)	Combined Sham (N=110)
Mean rate of change in GA area (mm) (square root transformation) from baseline to Month 12		
Least squares mean (SE)	0.29 (0.08)	0.40 (0.08)
Difference[a] (95% CI) p value[b]	**-0.11 (-0.19, -0.03)** **0.007**	
% Difference	**27.38**	
Mean rate of change in GA area (mm^2) (observed) from baseline to Month 12		
Least squares mean (SE)	1.59 (0.48)	2.29 (0.47)
Difference[a] (95% CI) p value	**-0.70 (-1.19, -0.20)** **0.006**	
% Difference	**30.45**	
Mean rate of change in GA area (mm) (square root transformation) from baseline to Month 18		
Least squares mean (SE)	0.43 (0.09)	0.60 (0.09)
Difference[a] (95% CI)	**-0.17 (-0.27, -0.07)**	
% Difference	**28.11**	
Mean rate of change in GA area (mm^2) (observed) from baseline to Month 18		
Least squares mean (SE)	2.43 (0.61)	3.59 (0.59)
Difference[a] (95% CI)	**-1.16 (-1.83, -0.48)**	
% Difference	**32.24**	

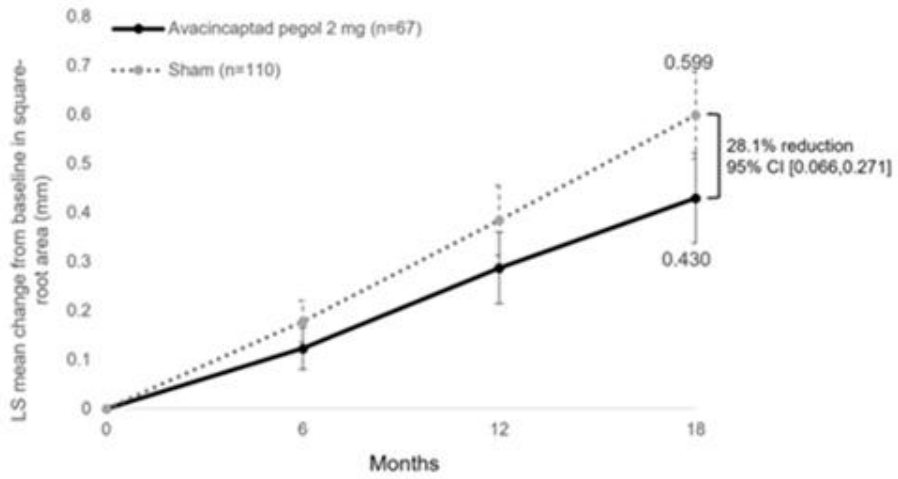
Source: Table 2.5-1, p108 of the submission; Table 18 and Table 19, pp95,96 and 98 of the GATHER1 Clinical Study Report (CSR)
ACP = avacincaptad pegol; CI = Confidence interval; GA = geographic atrophy; ITT = Intent-to-treat; mm = Millimetre; SE = Standard error.
[a] Difference in least squares means between groups calculated as (sham) minus (ACP)
[b] % Difference is calculated by 100*(Difference)/(Least Squares Mean from Sham)
Note: The Advisory Committee on Medicines (ACM) confirmed that 'square root transformed atrophic area' is the most effective measure, reflecting linear lesion growth and reducing correlation with initial size.
Note: **Bold** indicates statistically significant results.

Figure 1: Mean rate of change in GA area from baseline to Month 12 in GATHER1 (study eye, ITT population)



Source: Figure 2.5-1, p109 of the submission; Figure 2, p97 of the GATHER1 CSR

Figure 2: Mean rate of change in GA area from baseline to Month 18 in GATHER1 (study eye, ITT population)



Source: Figure 2.5-3, p111 of the submission; Figure 3, p99 of the GATHER1 CSR

6.17 In GATHER1, a statistically significant reduction in the rate of GA growth (square root transformed and observed) at Month 12 was reported for ACP compared to the Sham group (difference in LS mean of -0.11, 95% CI -0.19 to -0.03). At Month 18, the result continued to show a reduction in the rate of GA growth (observed) in the ACP group compared to the Sham group (-0.17, 95% CI -0.27 to -0.07). As previously noted, the PBAC considered that it was reasonable to assume that protecting the structure of the eye by slowing growth of GA lesion will result in slower loss of functional vision than current care (Pegcetacoplan, November 2025 PBAC Meeting outcomes).

6.18 Results of the primary endpoint in GATHER2 are presented in Table 5, Figure 3, and Figure 4.

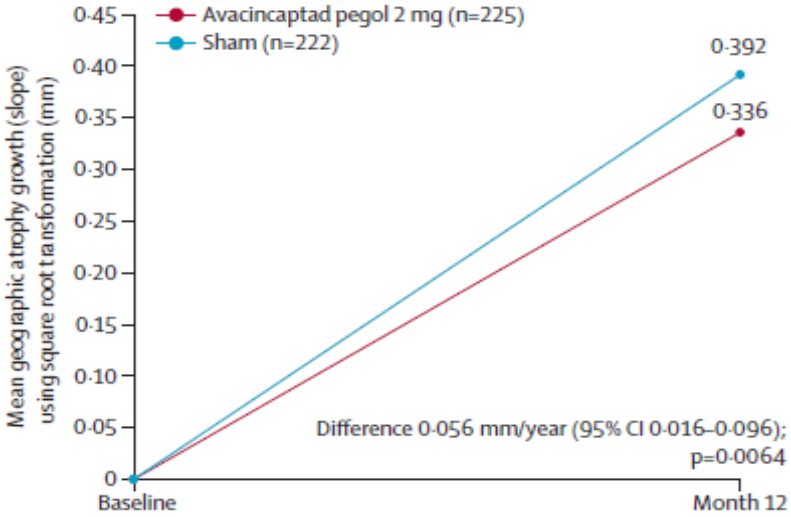
Table 5: Mean rate of GA growth per year from baseline to Month 12 and Month 24 (ITT; re-randomised population) in GATHER2

	ACP 2mg (N = 225)	Sham (N = 222)
Mean rate of GA growth (mm/year) (slope; square root transformed) from baseline to Month 12 (ITT)[a]		
Mean (SE)	0.34 (0.03)	0.39 (0.03)
Difference[b] (95% CI) p value	**-0.06 (-0.096, -0.016)** **0.006**	
% Difference[c]	**14.25**	
Mean rate of GA growth (mm^2/year) (slope; observed) from baseline to Month 12 (ITT)[a]		
Mean (SE)	1.75 (0.20)	2.12 (0.21)
Difference[b] (95% CI) p value	**-0.38 (-0.63, -0.12)** **0.004**	
% Difference[c]	**17.70**	
Mean rate of GA growth (mm^2) (observed) from baseline to Month 12 (ITT)[a]		
Mean (SE)	1.94 (0.22)	2.34 (0.22)
Difference[a] (95% CI) p value	**-0.41 (-0.67, -0.14)** **0.003**	
% Difference[c]	**17.0**	
Mean rate of GA growth (mm^2/year) from baseline (slope) to Month 24 (ITT)		
Mean rate (SE)	2.17 (0.08)	2.59 (0.08)

	ACP 2mg (N = 225)		Sham (N = 222)	
Difference[a] (95% CI) p value	**-0.42 (-0.65, -0.19)** **0.0004**			
% Difference[c]	**16.20**			
Mean change in GA area (mm²) (observed) from baseline to Month 24 (ITT)				
Least squares mean (SE)	4.43 (0.18)		5.42 (0.17)	
Difference[b] (95% CI) p value	**-0.99 (-1.48, -0.50)** **< 0.0001**			
Mean rate of GA growth (mm²/year) (slope) from baseline to Month 24 (re-randomised set)				
	ACP 2 mg EM (N = 96)	**Sham (N = 203)**	**ACP 2 mg EOM (N = 93)**	**Sham (N = 203)**
Growth rate (SE)	2.23 (0.12)	2.59 (0.09)	2.10 (0.13)	2.59 (0.09)
Difference[d] (95% CI) p value	**-0.36 (-0.66, -0.07)** **0.02**		-0.49 (-0.79, -0.19) 0.002[e]	
% Difference	**13.97**		18.85	

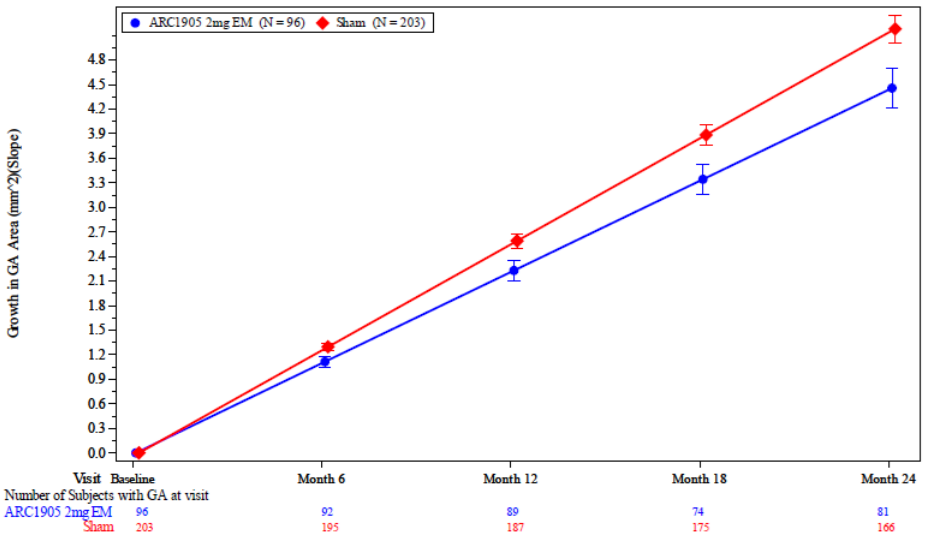
Source: 2.5-6, Table pp119-120 of the submission; Table 12, p65 of the GATHER2 CSR; Table 14.2.1.3a, Table 14.2.1.3b, Table 14.2.1.7a of the Table 14.2.1.7b, Table 14.2.2.1b of the GATHER2 CSR; Khanani AM et al (2023).
ACP = avacincaptad pegol; CI = Confidence interval; EM = Every month; EOM = Every other month; GA = geographic atrophy; ITT = Intent-to-treat; mg = Milligram; mm = Millimetre; SE = Standard error.
[a] Result from the GATHER2 primary efficacy analysis at Month 12 (Khanani AM et al. *Lancet* 2023; 402: 1449-1458)
[b] Difference in least squares mean growth rate between groups calculated as (sham) minus (ACP 2 mg).
[c] % Difference is calculated by 100*(Difference)/(Growth rate from sham).
[d] Difference in growth rate between groups calculated as (sham) minus (ACP 2 mg EM or EOM).
[e] p value for the comparison between ACP EOM vs. sham is nominal.
Note: The Advisory Committee on Medicines (ACM) confirmed that 'square root transformed atrophic area' is the most effective measure, reflecting linear lesion growth and reducing correlation with initial size.
Note: **Bold** indicates statistically significant results.

Figure 3: Mean rate of GA growth (square root-transformation; slope analysis) from baseline to Month 12 in GATHER2 (ITT population)



Source: Figure 2.5-10, p121 of the submission; Khanani et al (2023)

Figure 4: Mean rate of GA growth (observed, slope analysis) from baseline to Month 24 in GATHER2 (re-randomised population)



Source: Figure 2.5-11, p122 of the submission; Figure 2, p65 of the GATHER2 CSR

6.19 In GATHER2, a statistically significant reduction of mean rate of GA growth at Month 12 (difference in mean -0.06, 95% CI -0.096 to -0.016) and Month 24 (-0.42, 95% -0.65 to -0.19) was reported for the ACP group compared to the Sham group. However, after re-randomisation, both the EM and EOM groups were compared against a pooled Sham group, and while EM demonstrated a statistically significant benefit (-0.36, 95% CI 0-0.66 to -0.07), the EOM comparison was only nominal (-0.49, 95% CI -0.79 to - 0.19), showing numerically better outcomes without formal statistical confirmation. This approach does not robustly establish equivalence of effectiveness between EM and EOM dosing, as comparative accuracy would require a direct head-to-head analysis between EM and EOM groups rather than relying on separate comparisons to Sham. Consequently, the claim of similar efficacy for EOM is based on indirect inference rather than rigorous statistical evidence, contributing to uncertainty of benefits.

6.20 Results of the secondary efficacy endpoints — BCVA and low luminance-BCVA (LL-BCVA]) (ETDRS letters) in GATHER1 and GATHER2 are presented in Table 6.

Table 6: Results of BCVA and LL-BCVA (ETDRS letters) at Month 18 in GATHER1 and Month 24 in GATHER2 (ITT population)

GATHER1		
	Combined ACP 2mg (N=67)	**Combined Sham (N=110)**
Mean rate of change in BCVA (ETDRS letters) from baseline to Month 18		
Least squares mean (SE)	-12.7 (4.29)	-15.1 (4.12)
Difference[a] (95% CI)	2.37 (-2.23, 6.96)	
Mean rate of change in LL-BCVA (ETDRS letters) from baseline to Month 18		
Least squares mean (SE)	-2.72 (4.21)	-3.10 (4.03)
Difference[a] (95% CI)	0.37 (-4.10, 4.84)	
GATHER2		
	ACP 2mg (N=225)	**Sham (N=222)**
Mean rate of change in BCVA (ETDRS letters) from baseline to Month 24		
Least squares mean (SE)	-7.31 (1.07)	-6.48 (1.05)
Difference[a] (95% CI) p value	-0.83 (-3.79, 2.12) 0.58	
Mean rate of change in LL-BCVA (ETDRS letters) from baseline to Month 24		
Least squares mean (SE)	-10.58 (1.20)	-9.1 (1.18)
Difference[a] (95% CI) p value	-1.49 (-4.79, 1.81) 0.38	

Source: Table 2.5-2 & Table 2.5-3, pp113-114 of the submission; Table 20, Table 21, Table 22 & Table 23, pp100-105 of the GATHER1 CSR; Table 2.5-7 & Table 2.5-8, pp123-124 of the submission; Table 14 & Table 15, pp73-74 of the GATHER2 CSR; Khanani et al 2023.
ACP = avacincaptad pegol; BCVA = Best corrected visual acuity; CI = Confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; ITT = Intent-to-treat; LL-BCVA = Low luminance best corrected visual acuity; mg = Milligram; MMRM = Mixed model for repeated measures; SE = Standard error.

6.21 Treatment with ACP 2 mg for 18 months in GATHER1 and 24 months in GATHER2 did not result in a statistically significant difference in visual acuity in patients in either trial.

6.22 The National Eye Institute Visual Functioning Questionnaire (VFQ)-25 score[17], was used to assess quality of life in study patients in GATHER1 and GATHER2. Four subscales in VFQ-25 were considered of interest in both trials: near vision activities, distance vision activities, dependency, and role difficulties. Overall, results of the patient reported outcomes in GATHER1 and GATHER2 did not demonstrate an improved quality of life in patients treated with ACP 2 mg IVT for up to 24 months compared to Sham. In some of the VFQ-25 subscales, ACP 2 mg treated patients even showed worse performance related to functional vision, compared to Sham patients. Nevertheless, the validity of the VFQ-25 questionnaire has been controversial since several subscales, such as the general vision, colour vision, and peripheral vision, are single-item subscales (i.e., having limited response options) and therefore, the tool

[17] National Eye Institute Visual Functioning Questionnaire -25 (VFQ-25). URL: https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/vfq/vfq25survey_selfadmin.pdf. Higher score represents better function.

has been criticised as not being sensitive enough to capture small but clinically meaningful changes[18].

Indirect comparison of ACP vs pegcetacoplan — efficacy

6.23 In the anchored MAIC of OAKS vs GATHER2, the adjusted difference in GA lesion growth at Month 12 between pegcetacoplan EOM and ACP monthly was -0.540 mm^2 (95% CI: -1.397, 0.317; p = 0.22). In the anchored MAIC of DERBY vs GATHER2, the adjusted difference was -0.130mm^2 (95% CI: -1.425, 1.166; p = 0.85). The results numerically favoured pegcetacoplan EOM treatment. Meta-analysis showed the pooled effect for pegcetacoplan EOM (OAKS and DERBY) vs ACP monthly (GATHER2) was -0.415 mm^2 (95% CI: -1.13, 0.30; p = 0.25), directionally favouring pegcetacoplan EOM treatment.

6.24 The ESC noted the limitations of the MAIC include the following:

- For this indirect comparison, individual patient data (IPD) were available for OAKS and DERBY but not for GATHER2. As such, patient-level adjustments between the trials were not possible.
- Despite the matching of some enrolment criteria and key ocular variables between the trials, residual differences remained in study design and other enrolment criteria which could not be adjusted.
- The robustness of the results may have been affected by the small effective sample size in OAKS and DERBY for comparison, which is common in a MAIC and is the result of the trade-off for the number of matching variables.
- Data from GATHER1 were not included for comparison due to its incomparable trial design, mainly, the two-part trial design, and a key baseline variable (GA lesion focality) not being reported but was required for matching in the MAIC[19].
- Compared to the GATHER2 GA population, the OAKS and DERBY GA populations were heterogeneous with less residual functional vision and a more urgent need for effective treatment to preserve the residual functional vision. The results of the MAICs reflected a 'GATHER2-like' population, which is in fact a narrower GA population. The applicability of the results to the Australian setting is uncertain.

6.25 Results of the ML-NMR ITC which was informed by the GATHER1, GATHER2, DERBY, OAKS and FILLY trials are presented in Figure 5 and Figure 6. In the submission, it was stated that the transitivity assumption of the ML-NMR[20], event rates in the common reference groups, and factors that may cause heterogeneity of comparative treatment effects were addressed in detail in the Astella ITC Technical report. However, this

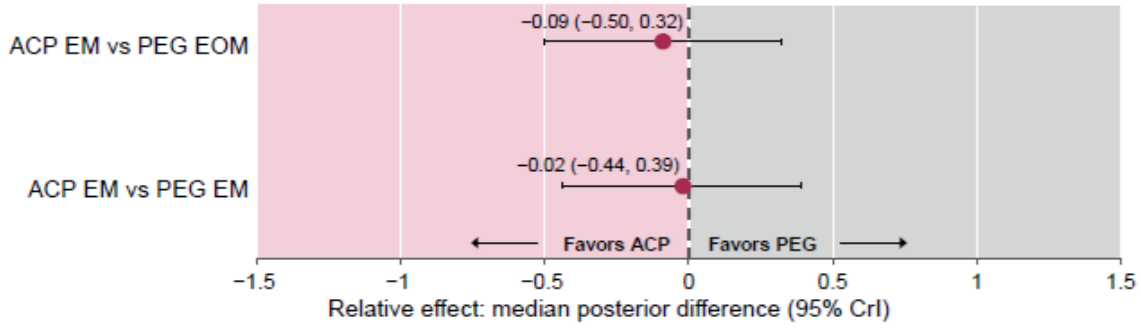
[18] Marella M, Pesudovs K, Keeffe JE et al. The psychometric validity of the NEI VFQ-25 for use in a low-vision population. *Invest Ophthalmol Vis Sci* 2010; 51(6): 2878-2884.

[19] Hahn P, Eichenbaum D, Dhoot D et al. Efficacy of intravitreal pegcetacoplan vs avacincaptad pegol in patients with geographic atrophy. *J Vitreoretin Dis* 2025. DOI 10.1177/24741264251379842

[20] Phillippo DM, Dias S, Ades AE et al. Multilevel network meta-regression for population-adjusted treatment comparisons. *J R Stat Soc Ser A Stat Soc* 2020;183(3):1189-1210.

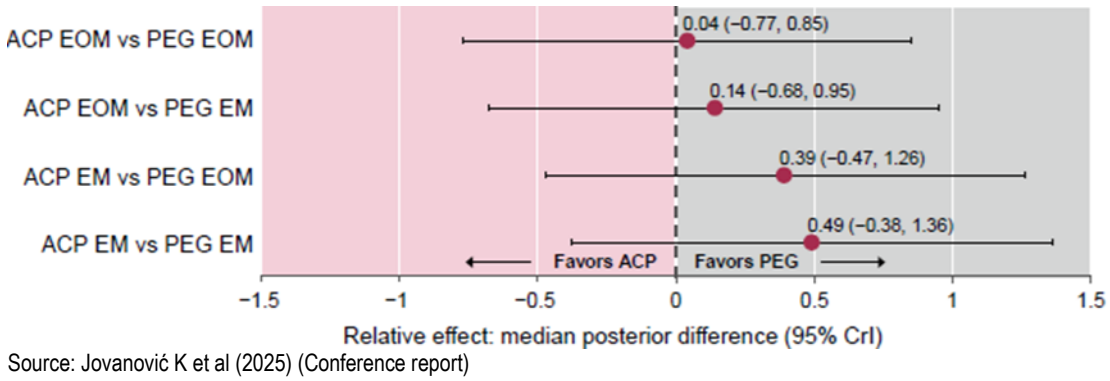
technical report was not available during the evaluation. The ESC noted the Astella ITC Technical report was provided with the PSCR. The ESC noted the technical report provided details on the adjustment variables used which included minimum distance to foveal centre, baseline GA lesion area, low-luminance deficit, lesion laterality, lesion focality, age and gender. The ESC noted the technical report also acknowledged the limitations of the analysis which included the low number of studies, unidentified or unreported effect modifiers and missing information on the correlation structure in aggregate studies. The ESC considered the use of ML-NMR ITC model to be novel but noted that it builds on existing model structures and has been published in a peer-reviewed statistical journal.

Figure 5: ML-NMR relative effect of ACP monthly vs pegcetacoplan monthly or every other month for the change from baseline in GA lesion size at Month 12



Source: Jovanović K et al (2025) (Conference report)
ACP = avacincaptad pegol; EM = every month; EOM = every other month; GA = geographic atrophy; ML-NMR = multi-level network meta-regression; PEG = pegcetacoplan
Note: PEG EOM was the near market comparator in the submission

Figure 6: ML-NMR relative effect of ACP monthly or every other month vs pegcetacoplan monthly or every other month for the change from baseline in GA lesion size at Month 24



Source: Jovanović K et al (2025) (Conference report)
ACP = avacincaptad pegol; EM = every month; EOM = every other month; GA = geographic atrophy; ML-NMR = multi-level network meta-regression; PEG = pegcetacoplan
Note: PEG EOM was the near market comparator in the submission

6.26 The result of relative effect of monthly ACP vs pegcetacoplan EOM for the change from baseline in GA lesion size at Month 12 directionally favoured monthly ACP. The relative effect of monthly ACP vs pegcetacoplan EOM for the change from baseline in GA lesion size at Month 24 directionally favoured pegcetacoplan EOM. The PSCR argued that post 12 months the ACP EOM dosing comparisons are the most applicable as it is the

expected dosing modality for both agents. The PSCR also noted that ACP showed similar efficacy relative to pegcetacoplan in slowing the decline in NL-BCVA at Month 12, 18, and Month 24, as well as LL-BCVA at Month 12. The ESC noted that the evidence base for ACP at 24 months of treatment is limited to just one study, which is reflected in greater uncertainty and wider 95% CIs in analyses at 24 months compared to 12 months. The ESC considered that the use of multiple subgroups across multiple outcomes and timepoints made the overall interpretation of the comparison between ACP and pegcetacoplan challenging. However, on balance, the ESC considered that it does not appear that one agent is clearly superior to the other.

6.27 In the NMR which included ten RCTs of five complement inhibitors, the Surface Under the Cumulative Ranking Curve (SUCRA) analysis indicated that monthly ACP 2 mg was the highest ranked for GA lesion size change (SUCRA = 93.55), followed by pegcetacoplan monthly (SUCRA = 81.37), with pegcetacoplan EOM being the lowest-ranked treatment option (SUCRA = 70.16). None of the treatment regimens demonstrated significant changes in BCVA compared to sham. The indirect comparison between the different interventions indicated that pegcetacoplan EOM was the highest ranked treatment option for BCVA (SUCRA = 90.49), followed by CLG561&LFG316(SUCRA = 65.75), and pegcetacoplan monthly (SUCRA = 63.43).

6.28 The ESC noted the limitations of the NMR method include the limited number of studies for analyses; the heterogeneity in the patient populations, study design, and statistical methods across studies, as well as the patient age and lesion location in different studies. Additionally, the short duration of the studies meant that changes in BCVA were unlikely to occur to a meaningful extent.

Comparative harms

6.29 A summary of the overall safety for a 12-month treatment period of the pooled data from GATHER1 and GATHER2 is presented in Table 7.

Table 7: Overall summary of treatment emergent adverse events (TEAEs) in patients receiving monthly ACP 2 mg IVT (pooled GATHER1 and GATHER2) vs sham (pooled GATHER1 and GATHER2) for 12 months (Safety population)

	ACP 2 mg (N = 292)[a]	Sham (N = 332)[b]	RD (95% CI)	RR (95% CI)
Any TEAE, n (%)	232 (79.5%)	231 (69.6%)	0.10 (0.03, 0.17)	1.14 (1.04, 1.25)
TEAE related to injection, n (%)	85 (29.1%)	69 (20.8%)	0.08 (0.02, 0.15)	1.40 (1.06, 1.85)
TEAE related to study drug, n (%)	4 (1.4%)	2 (0.6%)	0.01 (-0.01, 0.021)	2.27 (0.42, 12.33)
Any ocular TEAE (study eye) , n (%)	149 (51.0%)	121 (36.4%)	0.15 (0.07, 0.22)	1.40 (1.17, 1.68)
Ocular TEAE related to injection (study eye) , n (%)	84 (28.8%)	69 (20.8%)	0.08 (0.01, 0.15)	1.38 (1.05, 1.83)
Ocular TEAE related to study drug (study eye) , n (%)	4 (1.4%)	2 (0.6%)	0.01 (-0.01, 0.02)	2.27 (0.42, 12.33)
Any serious TEAE, n (%)	37 (12.7%)	57 (17.2%)	-0.05 (-0.10, 0.01)	0.74 (0.50, 1.08)
Any serious TEAE in study eye, n (%)	2 (0.7%)	2 (0.6%)	0.00 (-0.01, 0.01)	1.14 (0.16, 8.02)
Serious ocular TEAE related to injection (study eye), n (%)	0	0	0	-
Serious ocular TEAE related to study drug (study eye), n (%)	1 (0.3%)	0	0.00 (-0.00, 0.01)	-
Any severe TEAE[c]	38 (13.0%)	37 (11.1%)	0.02 (-0.03, 0.07)	1.17 (0.76, 1.79)
Any severe ocular TEAE[c] in study eye, n (%)	7 (2.4%)	2 (0.6%)	0.02 (-0.00, 0.04)	3.98 (0.83, 19.01)
Severe ocular TEAE[c] related to injection (study eye), n (%)	4 (1.4%)	0	0.01 (0.00, 0.03)	-
Severe ocular TEAE[c] related to study drug (study eye), n (%)	1 (0.3%)	0	0.00 (-0.00, 0.01)	-
Any TEAE leading to study drug discontinuation, n (%)	6 (2.1%)	3 (0.9%)	0.01 (-0.00, 0.03)	2.27 (0.57, 9.01)
Ocular TEAE leading to study drug discontinuation (study eye), n (%)	2 (0.7%)	0	0.01 (-0.00, 0.02)	-
TEAE leading to death, n (%)	2 (0.7%)	1 (0.3%)	0.00 (-0.01, 0.02)	2.27 (0.21, 24.95)

Source: compiled during evaluation; Table 33, p146 of the GATHER1 CSR; Khanani AM et al, Table 3.
ACP = avacincaptad pegol; CI = Confidence interval; IVT = Intravitreal; mg = Milligram; RD = Risk difference; RR = Risk ratio; TEAE = Treatment-emergent adverse event.
[a] All patients in GATHER1 and GATHER2 who were randomised to receive monthly ACP 2 mg IVT injection for ≥ 1 dose
[b] All patients in GATHER1 and GATHER2 who were randomised to receive monthly sham
[c] Severe AE refers to incapacitating AE that results in loss of ability to work or engage in usual activity
Note: RD and RR were developed by evaluator using Stata.

6.30 Overall, over a 12 month period, ACP treated patients experienced higher incidences in overall TEAEs and injection procedure-related TEAEs which were statistically significant, compared to Sham patients. ACP treated patients also experienced higher incidences in overall ocular TEAEs and injection-related ocular TEAEs (including severe TEAE) in the study eye, which were statistically significant, compared to patients receiving Sham treatment.

6.31 The most commonly reported (≥ 2%) ocular TEAEs in the GATHER1 and GATHER2 pooled data were conjunctival haemorrhage (16.8%), increased intraocular pressure (IOP) (12.3%), CNV (11.6%), punctate keratitis (8.2%), eye pain (5.8%), visual impairment (3.4%), blurred vision (3.1%), retinal haemorrhage (3.1%), vitreous floaters (3.1%), ocular hypertension (2.7%), blepharitis (2.4%), transiently reduced visual acuity (2.1%), and corneal abrasion (2.1%).

6.32 A summary of the overall safety at 24 months in GATHER2 is presented in Table 8.

Table 8: Overall summary of TEAEs in patients receiving ACP 2 mg and sham in GATHER2 at 24 months (Re-randomised population and Safety population)

	Re-randomised population			Safety population	
	ACP 2 mg EM N = 96	ACP 2 mg EOM N = 93	Sham N = 203	ACP 2 mg N = 225	Sham N = 222
Any TEAE, n (%)	89 (92.7)	89 (95.7)	167 (82.3)	208 (92.4)	184 (82.9)
TEAE related to injection, n (%)	37 (38.5)	31 (33.3)	41 (20.2)	84 (37.3)	47 (21.2)
TEAE related to study drug, n (%)	5 (5.2)	2 (2.2)	2 (1.0)	7 (3.1)	2 (0.9)
Any ocular TEAE (study eye), n (%)	67 (69.8)	60 (64.5)	99 (48.8)	144 (64.0)	107 (48.2)
Ocular TEAE related to injection (study eye), n (%)	37 (38.5)	31 (33.3)	41 (20.2)	83 (36.9)	47 (21.2)
Ocular TEAE related to study drug (study eye), n (%)	5 (5.2)	2 (2.2)	2 (1.0)	7 (3.1)	2 (0.9)
Any serious TEAE, n (%)	25 (26.0)	25 (26.9)	44 (21.7)	60 (26.7)	51 (23.0)
Any serious TEAE in study eye, n (%)	3 (3.1)	1 (1.1)	2 (1.0)	4 (1.8)	2 (0.9)
Any severe TEAE[a]	21 (21.9)	24 (25.8)	35 (17.2)	54 (24.0)	41 (18.5)
Any severe ocular TEAE[a] in study eye, n (%)	7 (7.3)	3 (3.2)	2 (1.0)	11 (4.9)	2 (0.9)
Any TEAE leading to study drug discontinuation, n (%)	3 (3.1)	2 (2.2)	7 (3.4)	11 (4.9)	9 (4.1)
Ocular TEAE leading to study drug discontinuation (study eye), n (%)	1 (1.0)	0	0	4 (1.8)	0
TEAE leading to death, n (%)	1 (1.0)	1 (1.1)	5 (2.5)	4 (1.8)	5 (2.3)

Source: Table 19, p83 of the GATHER2 CSR.
ACP = avacincaptad pegol; EM = Every month; EOM = Every other month; mg = Milligram; TEAE = Treatment-emergent adverse event.
[a] Severe AE refers to incapacitating AE that results in loss of ability to work or engage in usual activity

6.33 The safety evaluation over a 24-month treatment period in GATHER2 found ACP patients experienced more frequent serious TEAEs and severe ocular TEAEs in the study, compared to patients receiving Sham treatment. Four (1.8%) ACP patients had ocular TEAE leading to study drug discontinuation whereas this did not occur in the Sham treatment group.

6.34 Comparing safety in the ACP 2 mg EM with EOM treatment groups, EM patients experienced slightly more frequent injection related ocular TEAEs and more frequent study drug related ocular TEAEs, compared to EOM patients. Serious ocular TEAE and severe ocular TEAE in the study eye occurred more frequently in EM patients compared to EOM patients. One EM patient experienced ocular TEAE in the study eye leading to discontinuation of study drug compared to none in the EOM patients.

6.35 In GATHER2, patients receiving ACP 2 mg EM treatment experienced higher incidences of CNV (16.7% with EM vs 9.7% with EOM), conjunctival hyperaemia (8.3% with EM vs 4.3% with EOM), cataract (9.4% with EM vs 5.4% with EOM), vitreous floaters (5.2% with EM vs 1.1% with EOM), transiently reduced visual acuity (5.2% with EM vs 1.1% with EOM), and AEs associated with procedural complications (5.2% with EM vs 1.1% with EOM), compared to EOM patients. Patient receiving EOM treatment experienced a higher incidence of retinal haemorrhage (6.5% with EOM vs 3.1% with EM) and reduced visual acuity (5.4% with EOM vs 1.0% with EM) compared to EM patients.

Overall, ACP 2 mg EM treatment was associated with slightly more frequent ocular TEAEs in the study eye compared to EOM treatment.

6.36 In the ACP PI, ACP treatment associated CNV (the term 'neovascular' [wet] AMD is used in the PI) in the treated eye constitutes a boxed warning. The safety profile of ACP in the PI is based on GATHER1 and GATHER2. Combining data from GATHER1 and GATHER2, ACP 2 mg IVT appeared to have a stronger association with the development of CNV in the treated eye during the first 12 months of treatment. However, both studies were of short duration and only short-term safety data were available for evaluation. ACP 2 mg EM treatment appeared to be associated with more frequent development of CNV in the treated eye compared to EOM treatment.

6.37 Among the adverse events of special interests (AESIs) in GATHER2, patients in the ACP group experienced 6 times higher rate of IOP ≥ 30 mmHg (12.4% in ACP vs 1.8% in Sham) and a higher rate of increased IOP requiring surgery (4.4% in ACP vs 0 in Sham), and 3 times higher rate of decreased/blurred vision (15.1% in ACP vs 5.0% in Sham).

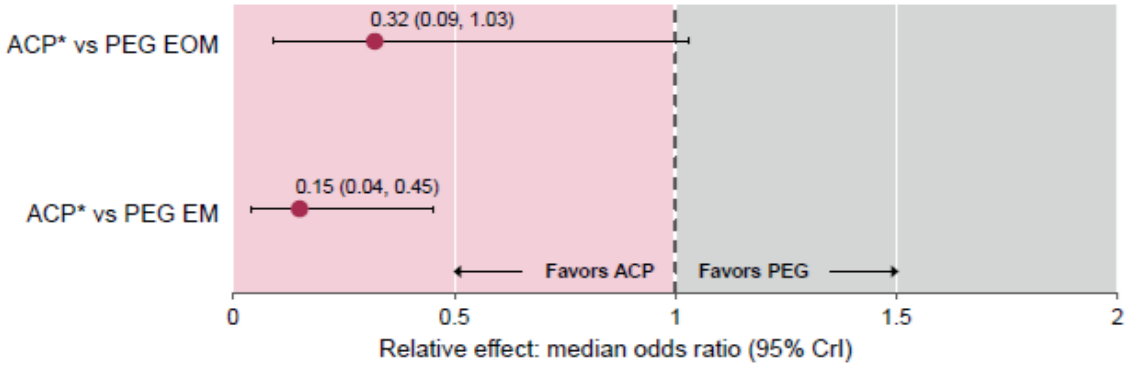
6.38 The PSCR noted the findings of an observational study from the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS) Registry reported a lower percentage of patients developing CNV than reported in the clinical trials. Inclusion was for patients aged ≥ 50 years who had received their first ACP injection between 2023 and 2024 and who had a prior diagnosis of GA. Of the 10,181 study patients, 3.6% of patients in 2.9% of eyes experienced a treatment emergent AE with 0.72% developing CNV.[21] The ESC noted these data were from a conference abstract.

Indirect comparison of ACP vs pegcetacoplan — safety

6.39 Results of the ML-NMR for the risk of experiencing new onset CNV are presented in Figure 7.

[21] *Borkar D, et.al. Treatment Patterns and Safety of ACP in Real World Patients with GA. Presented at: American Association of Ophthalmology 2025; Orlando, Florida, USA.*

Figure 7: ML-NMR relative effect of ACP vs pegcetacoplan for the risk of experiencing new onset CNV in study eye at Month 24



Source: Jovanović K et al (2025) (Conference report)
ACP = avacincaptad pegol; CNV = choroidal neovascularisation; EM = every month; EOM = every other month; GA = geographic atrophy; ML-NMR = multi-level network meta-regression; PEG = pegcetacoplan
* Including data from the ACP EM and EOM arms
Note: PEG EOM was the near market comparator in the submission

6.40 For the risk of new onset of CNV in study eye, CNV in the fellow eye at baseline was an important effect modifier. The indirect comparison of ACP and pegcetacoplan could not be adjusted for this effect modifier because no patients in GATHER1 or GATHER2 with baseline CNV in the fellow eye were enrolled. Therefore, the result of the indirect comparison between ACP EM/EOM vs pegcetacoplan EOM, which was based on two populations with different risk level of new onset of CNV in study eye at baseline, may have been biased. The PSCR acknowledged that confounding of the incidence of CNV during treatment is plausible due to baseline CNV in the fellow eye in pegcetacoplan trials. However, the PSCR clarified that the ML-NMR compared risks for ACP with the pegcetacoplan patients in whom CNV was absent at baseline. The ESC noted that the administration of pegcetacoplan EOM is the only regimen included in the TGA product information. The ESC also noted that, at 24 months, ACP was associated with higher odds of a serious ocular TEAE than pegcetacoplan EOM (median OR 1.61, 95% CI 0.14, 20.48).

6.41 In the NMR, among the treatments, ACP 2 mg was ranked highest for SAE (SUCRA = 82.31), followed by CLG561&LFG316 (SUCRA = 74.04), and CLG561 (SUCRA = 68.64). No treatments showed significant changes in SAE compared with sham. Pegcetacoplan monthly (odd ratio [OR]: 4.30, 95% credible interval [CrI]: 1.48, 16.72) increased the risk of CNV. ACP 2mg demonstrated favourable outcomes in terms of SAE and CNV. Due to the limitations of the NMR discussed in para 6.28, the evaluation considered the results of the NMR may not adequately support the claim in the submission that ACP is non-inferior to pegcetacoplan in terms of safety.

Benefits/harms

6.42 A summary of the comparative benefits and harms for ACP 2 mg vs BSC/sham in the GATHER1 and GATHER2 trials is presented in Table 9.

Table 9: Summary of comparative benefits and harms for ACP 2 mg vs sham/BSC in the GATHER1 and GATHER2 trials (ITT populations)

Benefits							
Continuous outcome							
GATHER1	**ACP 2 mg**			**Sham/BSC**			**Difference: ACP 2mg vs. BSC/sham (95% CI)**
	N	**LS Mean Δ baseline (mm^2)**	**SE**	**N**	**LS Mean Δ baseline (mm^2)**	**SE**	
Mean rate of change in GA area[a] (observed) from baseline to Month 12	67	1.59	0.48	110	2.29	0.47	-0.70 (-1.19. -0.20)
Mean rate of change in GA area[a] (observed) from baseline to Month 18	67	2.43	0.61	110	3.59	0.59	-1.16 (-1.83, -0.48)
GATHER2	**ACP 2 mg**			**Sham/BSC**			**Difference: ACP 2mg vs. BSC/sham (95% CI)**
	N	**Mean Δ baseline (mm^2/year)**	**SE**	**N**	**Mean Δ baseline (mm^2/year)**	**SE**	
Mean rate of GA growth[a] (slope, observed) from baseline to Month 12	225	1.75	0.20	222	2.12	0.21	-0.38 (-0.63, -0.12)
Mean rate of GA growth[a] (slope) from baseline to Month 24	225	2.17	0.08	222	2.59	0.08	-0.42 (-0.65, -0.19)
Harms							
	ACP 2 mg n/N[b]	**Sham/BSC n/N[c]**	**RR (95% CI)**	**Event rate/100 patients**			**RD (95% CI)**
				ACP 2 mg	**Sham/BSC**		
Adverse event between baseline and Month 12							
Any TEAE related to injection	85/292	69/332	1.40 (1.06, 1.85)	29.1	20.8		0.08 (0.02, 0.15)
Any ocular TEAE in the study eye	149/292	121/332	1.40 (1.17, 1.68)	51.0	36.4		0.15 (0.07, 0.22)
Any severe ocular AE in the study eye related to injection	4/292	0	N/A	1.4	0		0.01 (0.00, 0.03)
CNV in the study eye	21/292	12/332	1.99 (1.00, 3.97)	7.2	3.6		0.04 (-0.00, 0.07)

Source: Table 33, p146 of the GATHER1 CSR; Khanani AM et al, Table 3.
ACP = avacincaptad pegol; AE = Adverse event; BSC = Best supportive care; CI = Confidence interval; CNV = Choroidal neovascularisation; GA = geographic atrophy; ITT = Intent-to-treat; LS = Least squares; mg = Milligram; N/A = not applicable; RD = Risk difference; RR = Risk ratio; SE = Standard error; TEAE = Treatment-emergent adverse event.
[a] An increase in GA area implies worsening of disease
[b] Pooled patients in the ACP 2 mg arms in GATHER1 and GATHER2 who had received monthly ACP 2 mg IVT injection for ≥ 1 dose
[c] Pooled patients in the sham arms in GATHER1 and GATHER2 who had received monthly sham.
Note: RD and RR were calculated during the evaluation.

6.43 On the basis of direct evidence presented by the submission, the comparison of ACP 2 mg IVT in comparison to BSC/sham and over a treatment period of 12 months resulted in:

- A reduction in GA growth of between 0.34 to 0.70 mm^2 on average.

For every 100 patients treated:

- Approximately 15 additional patients would experience at least one ocular TEAE in the study eye.

- Approximately 1 additional patient would experience at least one severe ocular AE in the study eye related to injection.
- Approximately 4 additional patients would experience CNV in the study eye.

Clinical claim

6.44 The submission described ACP 2 mg IVT injection monthly as superior in terms of effectiveness compared to BSC/sham. The evaluation considered this claim was adequately supported but the magnitude of the benefit was uncertain. The key issue was that, although the submission demonstrated that ACP 2 mg dosed monthly or 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 visual acuity, in the proposed PBS population. The TGA Delegate's opinion was that GA area has emerged as an appropriate variable to assess progression of GA, especially in the earlier stages of the disease, since visual acuity will poorly reflect GA progression if the fovea remains unaffected. In its consideration of pegcetacoplan, the PBAC also previously considered that, although the clinical trials did not demonstrate clear improvements in vision related activities, it was reasonable to assume that protecting the structure of the eye by slowing GA lesion growth will result in slower loss of functional vision than current care. Despite considerable uncertainty in the magnitude of this benefit on vision, the PBAC was satisfied that pegcetacoplan provides, for some patients, a significant improvement in efficacy over BSC (Pegcetacoplan, November 2025 PBAC Meeting outcomes). The ESC agreed with the evaluation that the claim of superior effectiveness was adequately supported but the magnitude of benefit was uncertain.

6.45 The submission described ACP 2 mg IVT injection monthly as non-inferior in terms of clinical effectiveness compared to pegcetacoplan 15 mg IVT injection every other month. The evaluation considered this claim was not supported by the totality of evidence from the indirect comparisons provided in the submission. The ESC noted that the technical report for the ML-NMR ITC was provided with the PSCR. The ESC considered the technical report provided more confidence in the methodological approach, however, as outlined in paragraph 6.26, the overall interpretation of the comparison between ACP and pegcetacoplan remained challenging. Overall, the ESC considered that it does not appear that one agent is clearly superior to the other.

6.46 The submission described ACP 2 mg IVT injection monthly as inferior in terms of safety compared to BSC/sham. The ESC agreed with the evaluation that this claim was adequately supported by the evidence provided in the submission.

6.47 The submission described ACP 2 mg IVT injection monthly as non-inferior in terms of safety compared to pegcetacoplan 15 mg IVT injection every other month. The evaluation considered this claim was not adequately supported by the evidence from the indirect comparisons provided in the submission. The key issue was that there was fundamental difference in terms of the risk of new onset CNV in treated eye at baseline between the ACP trial population and the pegcetacoplan trial population

which could not be adjusted for in the indirect comparison. The ESC noted the PSCR (p5) clarified that the ML-NMR compared risks for ACP with the pegcetacoplan patients in whom CNV was absent at baseline. Overall, the ESC considered that a claim of non-inferior safety was uncertain but likely reasonable.

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

6.49 The PBAC considered that the claim of inferior comparative safety to BSC was reasonable.

6.50 The PBAC considered that the claim of non-inferior comparative effectiveness to pegcetacoplan was reasonable.

6.51 The PBAC considered that the claim of non-inferior comparative safety to pegcetacoplan was uncertain but likely reasonable.

Economic analysis

6.52 The submission presented a modelled economic evaluation based on the direct randomised trials, GATHER1 and GATHER2. The economic model assessed ACP compared to BSC in patients with GA secondary to AMD for patients who have an intact fovea and central vision threatened by GA growth. The clinical claim of superior effectiveness (in terms of reduced lesion growth) for ACP compared to BSC, in patients with intact fovea and central vision threatened by GA growth (i.e. the proposed PBS patient population) was established, however the magnitude of the clinical benefit (and extent of translation to patient-relevant outcomes) was uncertain.

6.53 Table 10 summarises the key components of the economic evaluation.

Table 10: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Avacincaptad pegol versus BSC
Time horizon	20 years (versus 18 months follow up in GATHER1)
Outcomes	Quality-adjusted life years
Methods used to generate results	Markov cohort analysis
Health states	Defined by GA lesion size (Small [< 7.5 mm²], Medium [7.5 – 12 mm²], or Large [12 – 17.5 mm²]) and distance to the foveal center (Far from foveal center [>0.25 mm] and Close from foveal center [≤ 0.25 mm]) Small- Far, Medium- Far, Large- Far, Small- Close, Medium- Close, Large- Close, Blind (defined as GA lesion size of ≥ 17.5 mm²) and Death These health states (based on lesion size and minimum distance to the foveal centre) are proxies for disease severity and risk of vision loss but do not directly measure functional vision or visual acuity and therefore may not correspond to clinically meaningful endpoints.
Cycle length	6 months
Transition probabilities	Transition probabilities for ACP and BSC were calculated by examining patient-level data from clinical trials at 6-month intervals over 18 months. These probabilities were estimated separately for ACP and BSC, without adjustments for patient characteristics, and were based on observed changes in GA area and distance to foveal centre.

Component	Summary
	Transition estimates come from a 7×7 matrix, based on small samples (N=47 ACP; N=73 BSC in GATHER1 trial). In the ACP group, there were no transitions into the 'Blind' health state except from 'Large, Far' and 'Large, Close' during the first cycle, which may influence the perceived effectiveness of the intervention. Because the sample size is limited and certain transitions are infrequent, there's increased uncertainty and reduced generalisability of findings. Mortality was informed by ABS lifetables in both arms with excess mortality applied to severe visual impairment health states. Vision impairment is linked to higher mortality risk in older populations, primarily through indirect mechanisms such as falls, depression, and reduced independence. The evaluation noted there was no strong evidence that GA lesion size directly influences mortality.
Extrapolation method	The model sets a maximum treatment duration of 3 years for ACP, after which all patients stop ACP and follow the BSC transition matrix for the rest of the model time horizon. To extrapolate ACP outcomes beyond the 18-month GATHER1 study, it is assumed that the treatment effect remains constant throughout active treatment, with transition probabilities from cycle 3 (13–18 months) applied until the end of treatment. GA progression is not linear; lesions grow faster as size increases, especially with foveal involvement. Applying cycle 3 transition probabilities over the entire time horizon assumes a constant risk, ignoring age-related acceleration and patient variability. With only 18 months of data informing 20-year projections, over 90% of transitions are extrapolated, likely underestimating long-term uncertainty.
Health related quality of life	Health state utilities are identical across the two arms, derived from a virtual reality assisted vignette-based time trade-off (TTO) study conducted among UK general population participants This study was designed to align with the economic model by defining GA severity using lesion area and proximity to the foveal centre, consistent with the model's health state structure. Difference in HRQoL for patients across the arms is driven by differences in health state transitions. No disutility associated with ACP administration was applied. TTO study vignettes, even when supported by virtual reality, assess hypothetical health states that may not fully capture the functional impact of GA. VFQ-25 responses, gathered during the trial, cover domains like mental health, dependency, and social functioning, which are difficult to reflect in vignettes. Overlooking these areas could lead to an incomplete or inaccurate assessment of HRQoL between treatment groups. Sensitivity analysis using VFQ-25-derived utilities, such as VFQ-UI or mapping, may improve study reliability
Costs	Costs included drug acquisition and administration cost of the ACP, disease management costs, AE management and one-time cost of blindness. According to the proposed listing and TGA product information, ACP dosing schedule in Year 2 onwards could be EM or EOM. The cost varies based on what dosing schedule is used. Base case model assumes EOM dosing schedule. ICER increased by [redacted]% when Year 2+ dosing schedule was changed to EM.

Source: Constructed during the evaluation based on Table 3.1-1, p174 of the submission.
ABS = Australian Bureau of Statistics; ACP = avacincaptad pegol; AE = Adverse event; BSC = Best supportive care; EM = Every month; EOM = Every other month; GA = geographic atrophy; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; mm = Millimetre; QoL = Quality of life; TGA = Therapeutic Goods Administration; TTO = time trade-off; UI = utility index; UK = United Kingdom; VFQ = Visual Function Questionnaire.

6.54 The model adopts a 20-year time horizon with a mean starting age of 78.8 years. The evaluation noted this was consistent with the PBAC guidelines which stipulate to capture all important differences in costs and outcomes, as ACP treatment was

modelled to affect mortality or long-term quality of life. However, the follow-up duration for the GATHER1 and GATHER2 trial was just 18 or 24 months and there are no additional external data to inform disease progression beyond this time period. Therefore, the extrapolations in the model are highly uncertain. The evaluation considered a truncated time horizon would reduce the uncertainty of long-term disease progression extrapolations. The PSCR argued that, as GA is a chronic, progressive, and irreversible condition associated with long-term vision loss and substantial downstream consequences a 20-year time horizon was appropriate. The ESC acknowledged the concerns raised by both the evaluation and the PSCR and considered a 15-year time horizon would be more appropriate. The PBAC noted this was consistent with pegcetacoplan (paragraph 7.15, pegcetacoplan Public Summary Document [PSD], November 2025 PBAC Meeting).

6.55 The structure of the economic model relied on the progression of vision loss classified by health states differentiated based on GA area (small, medium, large, blind) and minimum distance to the foveal centre (close or far). These states are proxies for disease severity and risk of vision loss but do not directly measure functional vision or visual acuity and may not correspond to clinically meaningful endpoints. During its evaluation of pegcetacoplan in November 2025, the PBAC noted that although clinical trials of pegcetacoplan did not confirm clear improvements in vision-related activities, preserving eye structure by slowing GA lesion progression could reasonably slow functional vision decline versus current treatments. Despite uncertainty about the magnitude and duration of this benefit, PBAC considered pegcetacoplan more effective than best supportive care for some patients. There remains doubt about how microperimetry results translate to real-world vision gains, and the sponsor's projected duration of benefit was viewed as overly optimistic (PBAC Meeting Outcomes, November 2025). The PSCR stated that GA lesion size and distance to the foveal centre point were used to define the model health states as their importance to vision loss, blindness and patient experience was validated in interviews with clinicians and patients. The ESC considered that translation of these clinical measures into functional and directly patient relevant outcomes required additional assumptions and outcome translations that, while reasonable in principle (as indicated by the PBAC in their consideration for pegcetacoplan), are associated with considerable uncertainty. The PBAC noted the mixed support from health care professionals in the input received via the Office of Health Technology Assessment Consultation Hub (see paragraph 6.4). The PBAC also noted that the structure of the pegcetacoplan economic model relied on the progression of vision loss classified by health states grouped by Early Treatment Diabetic Retinopathy Study (ETDRS) letters (paragraph 6.45, pegcetacoplan PSD, November 2025 PBAC Meeting). Thus, the PBAC noted it was not possible to directly compare the ACP and pegcetacoplan models. The PBAC noted the pegcetacoplan multivariate analysis accepted by the Committee reported an incremental QALY of 0.220 (see Table 13, pegcetacoplan PSD, November 2025 PBAC Meeting).

6.56 Transition probabilities for ACP and BSC were calculated by examining patient-level data from GATHER1 trial at 6-month intervals over 18 months (ACP treatment regimen of every month). These probabilities were estimated separately for ACP and BSC, without adjustments for patient characteristics, and were based on observed changes in GA area and distance to foveal centre. Concerns associated with the quantification of the surrogate-functional outcome relationship and the estimated treatment effect include:

- Transition estimates come from a 7×7 matrix, based on small samples of between 3 and 21 patients per health state (total study N=47 ACP; N=73 BSC). In the ACP group, except for a few patients transiting to the 'Blind' health state from 'Large, Far' and 'Large, Close' during the first cycle, there were no transitions into the 'Blind' health state in cycles 2 or 3. Because the sample size is limited and certain transitions likely to be infrequent, there is high uncertainty, low precision and reduced generalisability in the transition estimates. Furthermore, these health-state transitions serve as proxies for disease progression rather than necessarily representing distinct clinically validated outcomes. The PSCR argued that GATHER1 provided the longest period of continuous protocol follow-up (18 months), allowing for the most robust comparison of the treatment effect. The PSCR noted that the submission presented a scenario analysis which pooled GATHER1 and GATHER2 patient level data, thereby increasing the number of patients contributing to each health state (the pooling having a larger sample range of 12 to 87 patients). The PSCR noted that this scenario increased from the ICER from a base case of $55,000 to < $75,000 per QALY gained to $75,000 to < $95,000 per QALY gained. The ESC considered it appropriate to pool the results of the GATHER1 and GATHER2 trial as presented in the scenario analysis.
- The model sets a maximum treatment duration of 3 years for ACP, after which all patients stop ACP and follow the BSC transition matrix for the rest of the model time horizon. An annual treatment discontinuation risk of 19.9% (converted to per cycle discontinuation rate of 10.52%), based on data from the GATHER1 trial, was applied to patients receiving ACP. To extrapolate ACP outcomes beyond the 18-month GATHER1 study, it is assumed that the treatment effect remains constant throughout active treatment, with transition probabilities from cycle 3 (13–18 months) applied until the end of treatment. Currently, there is no longitudinal data available beyond 24 months for ACP. It was not appropriate to extend the assumption of the treatment effect beyond the period of its application as the determination of sustained treatment effect beyond the trial period remains uncertain. For the BSC group, the same cycle 3 transition probabilities are used for rest of the entire model period.
- GA progression is nonlinear; lesions grow faster as they enlarge, especially with foveal involvement. The model's approach of applying cycle 3 transition probabilities across the remaining time horizon assumes a constant risk profile. This is a significant limitation, as it overlooks both the age-related acceleration in

GA progression and the varied growth rates among patients (i.e., fast versus slow progressors). Furthermore, as atrophy occurs, the negative impact on quality of life escalates disproportionately, suggesting that transition probabilities should ideally be dynamic, varying over time and according to lesion characteristics. Given that the model projects outcomes over a 20-year period based on only 18 months of observed data, more than 90% of the transitions are extrapolated using fixed cycle 3 transitions. The ESC considered a 15-year time horizon would be more appropriate.

- Mortality was informed by ABS lifetables in both arms with excess mortality applied to severe visual impairment health states. Blindness is linked to higher mortality risk in older populations, primarily through indirect mechanisms such as falls, depression, and reduced independence. There is no strong evidence that GA lesion size (and associated vision loss) itself directly influences mortality. Therefore, excess mortality applied to health states other than "Blind" was not justified in the submission. The PSCR argued that the results from Ahluwalia et al (2021)[22] supported the approach taken in the submission. Ahluwalia et al (2021) reported that patients with total GA area in the highest quartile had significantly higher risk of all-cause mortality compared with those in the lowest quartile (HR = 3.42, 95% CI 1.32, 8.86, p=0.011). The ESC noted that the results from Ahluwalia et al (2021) were a comparison within the GA population, with no comparison of mortality against the non-GA population. The ESC advised that excess mortality should only be applied to the "Blind" health state.

6.57 The utility values applied in the economic model differed by health state but were not treatment specific. No utility decrements were applied for ACP intravitreal injections. This may not be reasonable given intravitreal injections themselves often have a separate disutility in economic models (commonly –0.005 to –0.01 per injection), based on patient inconvenience, anxiety, and short-term discomfort. If injection disutility is not explicitly modelled, the analysis may underestimate treatment burden. The ESC advised that a utility decrement due to ACP administration should be included. The ESC considered that an appropriate utility decrement would be 100% daily utility loss for one day for 50% of patients per administration (as per NICE recommendation[23]).

6.58 The model incorporates disutilities for key treatment-related adverse events, CNV and IOP, observed in GATHER1. The model's assumption that CNV and IOP share the same QALY decrement (–0.06) underestimates the impact of CNV, which is clinically more severe and often associated with permanent vision loss and additional treatment

[22] Ahluwalia A, Shen LL, Chen EM, Sun M, Park MM, Young BK, Del Priore LV. Geographic atrophy severity and mortality in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2021 Sep;259(9):2643-2651. doi: 10.1007/s00417-021-05145-9. Epub 2021 Mar 19. PMID: 33742280

23 NICE guideline NG82, Appendix J: Health Economics

burden (e.g., anti-VEGF injections). Literature supports a higher QALY decrement for CNV (–0.07 to –0.12) and a lower QALY decrement for IOP (–0.01 to –0.03).

6.59 Health-related quality of life (HRQoL) utilities were derived from a vignette-based Time Trade-Off (TTO) study conducted among UK general population participants, rather than using trial-based National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) data collected in the pivotal studies GATHER1 and GATHER2. The vignettes, although supported by Virtual Reality experiences, rely on hypothetical descriptions and relatively brief interaction with the various health states, which may oversimplify the functional impact of GA and fail to capture nuances (such as mental health, dependency, and social functioning that would be revealed in VFQ-25 responses) identified by patients constantly living with GA. Consequently, despite the attempt to match to the model health states, invariably the TTO utilities are disconnected from observed trial outcomes, and this introduces some uncertainty and may affect the validity of the estimates. While vignette-based utilities are acceptable under PBAC guidelines, scenario analyses comparing vignette-derived utilities with VFQ-25 mapped to EQ-5D utilities would have ensured transparency and robustness in cost-effectiveness estimates.

6.60 ACP is dosed at 2 mg EM for the first year, then EM or EOM as per TGA-approved Product Information or the proposed PBS listing. The economic model used EOM (monthly in year one, then every other month) as the base case and EM (continuous monthly dosing) for scenario analysis, assuming similar efficacy for both regimens. In the GATHER2 trial, patients in the ACP arm were re-randomised to receive either EM or EOM dosing after 12 months, with efficacy assessed as the mean change in GA transformed area from baseline. Both EM and EOM groups were compared against a pooled Sham group, and while EM demonstrated a statistically significant benefit, the EOM comparison was only nominal, showing numerically better outcomes without formal statistical confirmation. This approach does not robustly establish equivalence between EM and EOM dosing, as comparative accuracy would require a direct head-to-head analysis between EM and EOM groups rather than relying on separate comparisons to Sham. Consequently, the claim of similar efficacy for EOM is based on indirect inference rather than rigorous statistical evidence, introducing uncertainty of benefits. The PSCR argued that advice from clinicians supported use of EOM in the base case. The PSCR also included utilisation data from the United States of America (August 2023 to November 2025) which indicated an average of 3.2 injections per patient eye in the first 6 months of treatment. The ESC considered that after the first 12 months of monthly ACP dosing a mixture of both EM and EOM dosing would likely occur in clinical practice with the choice of regimen depending on the prescriber and patient preferences. The ESC considered that it would be informative to model a 50:50 split of EM:EOM dosing after the first 12 months of EM treatment. The pre-PBAC response continued to argue that the utilisation data from the United States of America, along with local expert advice, supported EOM dosing as the preferred approach from Year 2 onwards.

6.61 The model assumes 100% compliance with the dosing schedule and an annual treatment discontinuation risk of 19.9% based on data from the GATHER1 trial was applied. The base case uses the EOM schedule, with scenario analysis for EM. The model sets a maximum treatment duration of 3 years for ACP, after which all patients stop ACP.

6.62 The estimated annual drug acquisition cost for ACP (EM) is [redacted] and for ACP (EOM) is [redacted]. The estimated annual costs per patient for ACP treatment including administration of intravitreal injection are [redacted] for EM regimen and [redacted] for EOM regimen.

6.63 The model also included costs associated with disease management, adverse events (CNV and IOP) and one-off cost of new blindness. The submission estimates CNV management costs based on the number of ranibizumab or aflibercept administrations in a single year, assuming patients receive treatment for only one year per CNV event before being re-exposed to CNV risk. This assumption is unlikely to reflect real-world clinical practice, as CNV is an incurable condition requiring ongoing treatment. Evidence from the Drug Utilisation Sub-Committee (DUSC) report (Predicted versus actual analysis of aflibercept, DUSC Report, October 2015) shows that most patients remain on anti-VEGF therapy for many years, with clinicians commonly using a “treat-and-extend” regimen. Therefore, limiting CNV treatment costs to one year significantly underestimates the true economic burden of managing this AE. The PSCR clarified that CNV costs are based on patient years of treatment rather than single year of treatment per patient. The mean annual number of aflibercept (7.0) and ranibizumab (8.8) injections was applied to patient-years of treatment. Patient-years were calculated by multiplying the number of patients by the average treatment duration of ACP treatment (2.08 years) used in the financial model. This corresponds to approximately 14.6 aflibercept injections and 18.3 ranibizumab injections per GA patient.

6.64 The key model drivers are presented in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Time horizon	The submission considered a 20-year time horizon in the base case analysis. The follow-up duration for the GATHER1 and GATHER2 trial was just 18 or 24 months and there are no additional external data to inform disease progression beyond this time period. Therefore, the extrapolations in the model based on the constant transition probabilities beyond 18 months are highly uncertain. The ESC considered a 15-year time horizon would be more appropriate.	Time horizon of 5 years increased the ICER by [redacted]%.
ACP dosing schedule	The base case analysis assumed every other month dosing schedule for ACP (EM in year 1 and EOM in Year 2+). According to the proposed listing and TGA product information, ACP dosing schedule in Year 2 onwards could be either every month (EM) or every other month (EOM). The cost per course per patient varies based on what dosing schedule is used. The ESC considered that it would be informative to model a 50:50 split of EM:EOM dosing after the first 12 months of EM treatment.	High, favours ACP. Choosing EM dosing schedule increased the ICER by [redacted]%.
Source of transition probabilities	The base-case analysis relied on transition probabilities (7×7 matrix) calculated from a relatively small subset of GATHER1 participants (N=47 for ACP and N=73 for BSC). Using pooled data from both GATHER1 and GATHER2 studies (N=223 for ACP and N=258 for BSC) does improve accuracy. However, even after combining samples, the overall group remains fairly small compared to the complexity of the model and the number of health states involved, resulting in greater uncertainty about the parameters and the possibility of having very few transitions observed for rare states (such as Large-Close or Blind). The ESC considered that pooled data should be used to inform the model.	Moderate, favours ACP. Using pooled data from GATHER1 and GATHER2 increased ICER by [redacted]%
Application of excess mortality	The submission applied excess mortality to severe visual impairment health states. This was not reasonable. Blindness is linked to higher mortality risk in older populations, primarily through indirect mechanisms such as falls, depression, and reduced independence. The ESC agreed with the evaluation that there is no strong evidence that GA lesion size directly influences mortality, therefore excess mortality should not be applied to all severe health states.	Moderate, favours ACP. Removing excess mortality application to the severe visual impairment health states increased ICER by [redacted]%.

Source: Constructed during the evaluation using Table 3.9-2,p213 of the submission and the "Attachment 11 – Izervay CE Model.xlsm" provided with the submission.

ACP = avacincaptad pegol; BSC = Best supportive care; EM = Every month; EOM = Every other month; GA = geographic atrophy; ICER = incremental cost-effectiveness ratio; QALY = Quality-adjusted life year; TGA = Therapeutic Goods Administration.

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

6.65 The results of a stepped analysis presented in the submission are summarised in Table 12. The stepped analysis shows that when the time horizon is increased to 20 years (Step 2), the modelled QALY outcomes reveal a larger difference between the two groups than with the trial-based 18-month time horizon (Step 1). This is because the model either rarely transitioned to poorer health states or didn't transition from other health states to the Blind health state—except in Cycle 1—while patients were on ACP treatment, leading to higher QALYs accrued in the ACP treatment arm.

Table 12: Results of the stepped economic evaluation presented in the submission

Step and component	ACP	BSC	Increment
Step 1: Costs and outcomes for study drug only (trial based 18-month time horizon)			
Costs	$[redacted]	$0	$[redacted]
QALYs	1.117	1.102	0.016
Incremental cost/extra QALY gained			$[redacted][1]
Step 2: Time horizon extended to 20 years incorporating excess mortality due to GA			
Costs	$[redacted]	$0	$[redacted]
QALYs	5.684	5.223	0.461
Incremental cost/extra QALY gained			$[redacted][2]
Step 3: Include discounting for costs and outcomes at 5% per annum			
Costs	$[redacted]	$0	$21,822
QALYs	4.431	4.078	0.353
Incremental cost/extra QALY gained			$[redacted][3]
Step 4: Include costs associated with disease and AE management and disutilities associated with AEs			
Costs	$[redacted]	$32,560	$[redacted][4]
QALYs	4.409	4.074	0.335
Incremental cost/extra QALY gained (base case)			**$[redacted][5]**

Source: Table 3.8-1, p208 of the submission.

ACP = avacincaptad pegol; AE = Adverse event; AEs = Adverse Events; BSC = Best supportive care; GA = geographic atrophy; QALY = Quality-adjusted life year; QALYs = Quality-adjusted life years.

The redacted values correspond to the following ranges:

[1] *$955,000 to < $1,055,000*

[2] *$45,000 to < $55,000*

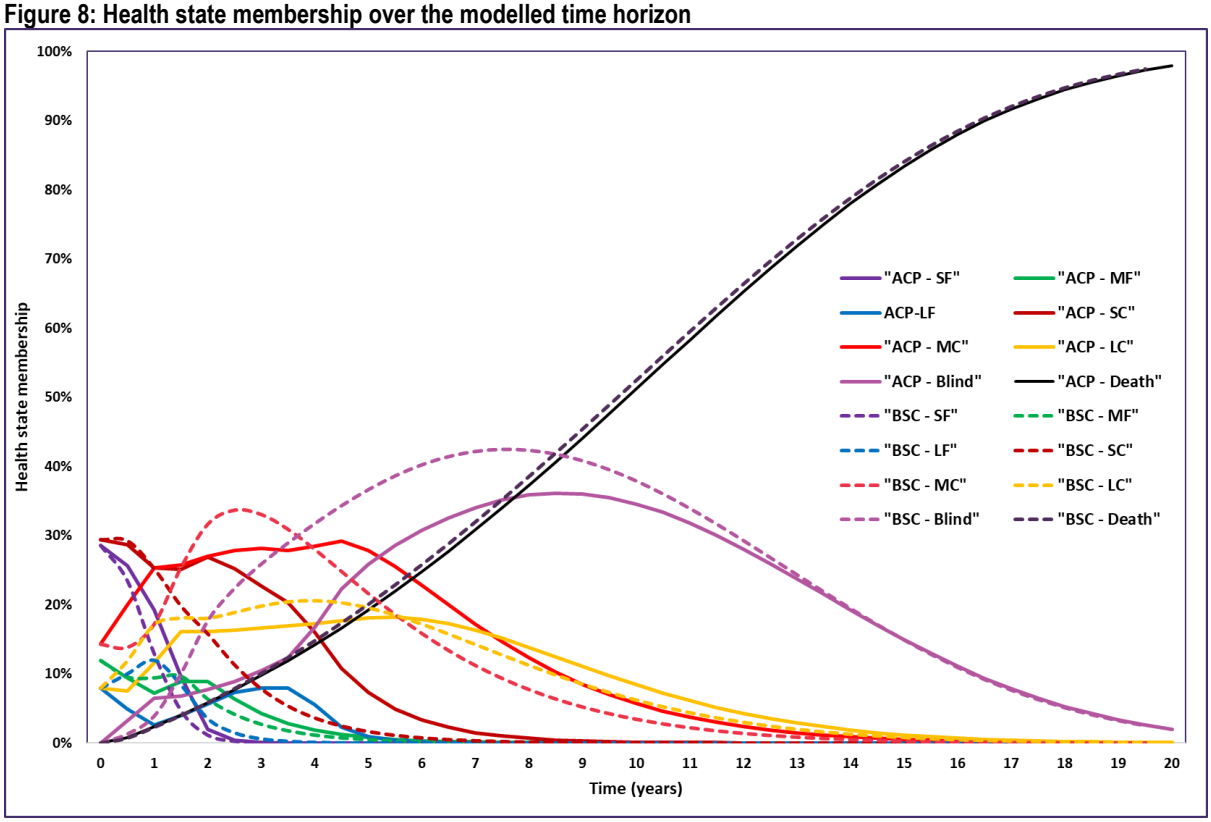
[3] *$55,000 to < $75,000*

[4] *$15,000 to < $25,000*

[5] *$55,000 to < $75,000*

6.66 Markov traces for the ACP and BSC arms are presented in Figure 8. Consistent with the model rationale, it is evident that patients who receive only BSC tend to progress to worse health states (e.g. with close lesions or blind) faster than those who receive ACP therapy, and the untreated population as a whole spends a longer time in these states than a population treated with ACP.

Figure 8: Health state membership over the modelled time horizon



Source: Constructed during the evaluation from the "Attachment 11 – Izervay CE Model.xlsm" attachment provided with the submission.
ACP = avacincaptad pegol; BSC = best supportive care; LC = Large, Close; LF = Large, Far; MC = Medium, Close; MF = Medium, Far; SC = Small, Close; SF = Small, Far.

6.67 The disaggregated and aggregated costs and outcomes are presented in Table 13 and Table 14.

Table 13: Disaggregated summary of cost impacts (discounted)

Resource item	ACP (EOM Year 2+)	BSC	Increment	% of total increment
Treatment costs				
ACP acquisition	$[redacted]	$0	$[redacted]	[redacted]%
ACP administration cost	$5,761	$0	$5,761	[redacted]%
Management of adverse events				
IOP	$12	$0	$12	[redacted]%
CNV	$5,589	$1,221	$4,368	[redacted]%
Medical resource use				
One-time cost of blindness	$287	$338	-$51	[redacted]%
Total cost, disease management	$29,990	$31,001	-$1,011	-[redacted]%
Request all %'s Small, Far	$743	$559	$184	[redacted]%
Medium, Far	$656	$589	$68	[redacted]%
Large, Far	$892	$700	$192	[redacted]%
Small, Close	$2,692	$1,575	$1,117	[redacted]%
Medium, Close	$7,080	$6,153	$927	[redacted]%
Large, Close	$5,166	$5,306	-$140	-[redacted]%
Blind	$12,760	$16,119	-$3,359	-[redacted]%
Overall total	**$[redacted]**	**$32,560**	**$[redacted]**	**100%**

Source: Table 3.8-2, p209 of the submission and the "Attachment 11 – Izervay CE Model.xlsm" provided with the submission.
ACP = avacincaptad pegol; BSC = Best supportive care; CNV = Choroidal neovascularisation; EOM = Every other month; IOP = Intraocular pressure.

Table 14: Disaggregated summary of average health outcomes

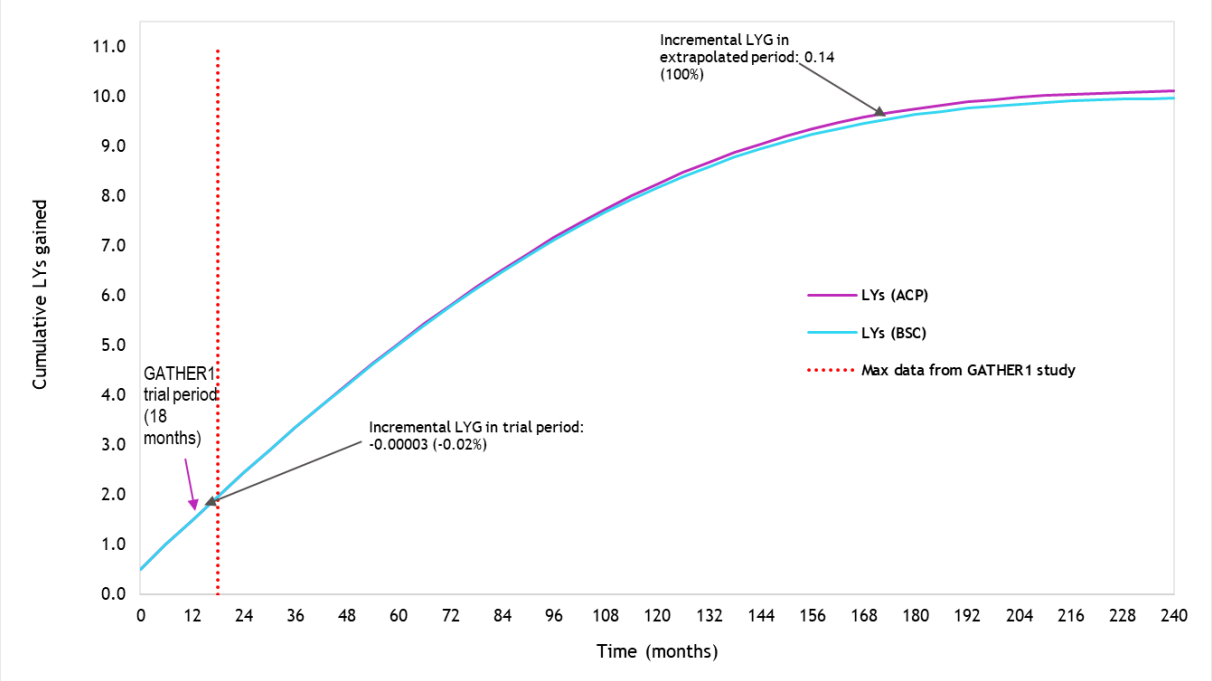
Outcome	ACP	BSC	Increment	% of total increment
LYs (undiscounted)				
Small, Far	0.284	0.213	0.071	51%
Medium, Far	0.265	0.234	0.030	22%
Large, Far	0.249	0.182	0.067	48%
Small, Close	1.115	0.629	0.487	347%
Medium, Close	2.164	1.843	0.321	229%
Large, Close	1.670	1.660	0.009	7%
Blind	3.852	4.698	-0.846	-604%
Total	**9.599**	**9.459**	**0.140**	**100%**
QALYs (discounted)				
Small, Far	0.232	0.175	0.057	17%
Medium, Far	0.205	0.184	0.021	6%
Large, Far	0.163	0.128	0.035	10%
Small, Close	0.834	0.488	0.346	103%
Medium, Close	1.294	1.124	0.169	51%
Large, Close	0.727	0.747	-0.020	-6%
Blind	0.976	1.233	-0.257	-77%
Adverse event				
• IOP AE	-0.004	0.000	-0.004	-1%
• CNV event	-0.018	-0.004	-0.014	-4%
Total	**4.409**	**4.074**	**0.335**	**100%**

Source: Table 3.8-3 and Table 3.8-4, p209 of the submission and the "Attachment 11 – Izervay CE Model.xlsm" provided with the submission
ACP = avacincaptad pegol; AE = Adverse event; BSC = Best supportive care; CNV = Choroidal neovascularisation; IOP = Intraocular pressure; LYs = Life-year; QALYs = Quality-adjusted life years.

6.68 ACP treatment costs account for most of the incremental costs between the two treatment groups. Treating CNV events also contributes to some of the incremental

costs, since more CNV events were observed in the ACP group. Most cost savings come from delaying or completely preventing patients from entering the "Blind" health state, which is more expensive to manage than other health states. The bulk of incremental QALYs accumulate in the "Small, Close," and "Medium, Close" health states because ACP patients remain in these health states longer than those on BSC. Similarly, fewer QALYs are associated with ACP in the "Blind" health state, reflecting the reduction of time in this state, as observed in costs. A gain of 0.14 undiscounted life years (equivalent to 0.088 discounted LYs) was generated in the extrapolated time period as shown in Figure 9. This small absolute LY gain generates approximately 9% of the total discounted QALY gain.

Figure 9: Cumulative life years gained over the model time horizon (undiscounted) (assuming vision loss increases mortality rate as per the submission)



Source: Constructed during the evaluation using the "Attachment 11 – Izervay CE Model.xlsm" provided with the submission.
ACP =avacincaptad pegol; BSC = best supportive care; LYs = life years gained; Max = maximum.

6.69 The results of key sensitivity analyses and multivariate analyses performed during the evaluation are summarised in Table 15. The model was most sensitive to the treatment regimen used and the time horizon. Base case ICER increased notably when time horizon, ACP dosing schedule, excess mortality application, and clinical efficacy data source were varied in multivariate analyses.

Table 15: Key sensitivity and multivariate analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Base case	**$[redacted]**	**0.335**	**$[redacted][1]**	**-**
Discount rate (base case: 5% costs and outcomes)				
• 0% costs and outcomes	$[redacted]	0.439	$[redacted][1]	-[redacted]%
• 3.5% costs and outcomes	$[redacted]	0.362	$[redacted][1]	-[redacted]%
Time horizon (base case 20 years)				
• 5 years	$[redacted]	0.205	$[redacted][2]	[redacted]%
• 10 years **(#1)**	$[redacted]	0.309	$[redacted][3]	[redacted]%
• 15 years (#2)	$[redacted]	0.332	$[redacted][3]	[redacted]%
ACP dosing schedule in Year 2+ (base case: every other month)				
• 50:50 EM:EOM dosing (#3)	$[redacted]	0.335	$[redacted][3]	[redacted]%
• EM dosing **(#7)**	$[redacted]	0.335	$[redacted][4]	[redacted]%
Excess mortality (base case: health state specific mortality HRs relative to general population)				
• Assume no excess mortality **(#4)**	$[redacted]	0.305	$[redacted][3]	[redacted]%
Source of efficacy data (base case: GATHER1)				
• Pooled data from GATHER1 and GATHER2 **(#5)**	$[redacted]	0.302	$[redacted][3]	[redacted]%
Utility decrement for ACP administration (base case: not applied)				
• 100% daily utility loss for one day for 50% of patients per administration **(#6)** [a]	$[redacted]	0.318	$[redacted][3]	[redacted]%
Multivariate analyses requested by the ESC				
#1 + #3 + #4 + #5	$[redacted]	0.262	$[redacted][2]	[redacted]%
#1 + #3 + #4 + #5 + #6	$[redacted]	0.238	$[redacted][5]	[redacted]%
#2 + #7 + #4 + #5	$[redacted]	0.274	$[redacted][5]	[redacted]%
#2 + #3 + #4 + #5	$[redacted]	0.274	$[redacted][2]	[redacted]%
#2 + #3 + #4 + #5 + #6	$[redacted]	0.251	$[redacted][5]	[redacted]%
Multivariate analyses requested by the PBAC				
#2 + EOM + #4 + #5 + #6	$[redacted]	0.274	$[redacted][3]	[redacted]%

Source: Constructed during the evaluation using Table 3.9-2,p213 of the submission and the "Attachment 11 – Izervay CE Model.xlsm" provided with the submission.

ACP = avacincaptad pegol; ICER = incremental cost-effectiveness ratio; QALY = Quality-adjusted life year.

[a] The utility decrement for ACP administration applied was 100% daily utility loss for one day for 50% of patients per administration, i.e. (baseline utility for the health state / 365.25 * 0.50). For EM treatment regimen there were 6 administrations and for EOM 3 administrations (NICE guideline NG82, Appendix J: Health Economics).

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$95,000 to < $115,000*

[3] *$75,000 to < $95,000*

[4] *$95,000 to < $115,000*

[5] *$115,000 to < $135,000*

6.70 The ESC requested a multivariate analysis that:

- reduced the time horizon from 20-years to 15-years;
- assumed 50:50 EM:EOM dosing for ACP in Year 2 onwards;

- removed the application of excess mortality from the severe visual impairment health states;
- pooled data from GATHER1 and GATHER2; and
- applied a utility decrement for ACP administration.

The ESC noted that this multivariate analysis increased the base case ICER from $55,000 to < $75,000 per QALY gained to $115,000 to < $135,000 per QALY gained. The ESC considered that this multivariate analysis addressed the key concerns raised by the Committee and that it was appropriate as a revised base case.

6.71 The PBAC requested an additional multivariate analysis which used the above parameters requested by ESC, with dosing reflecting the submission base case of EM in the first 12 months followed by EOM from year 2 onwards. This multivariate analysis increased the base case ICER from $55,000 to < $75,000 per QALY gained to $75,000 to < $95,000 per QALY gained.

Avacincaptad pegol cost/patient/year

Table 16: Avacincaptad pegol cost per patient for proposed and comparator drugs

	GATHER1 trial (follow-up 18 months)	**Economic model (maximum modelled treatment duration: 3 years)**	**Financial estimates**
Dosing schedule	Every month (EM)	Year 1: Every month (12 injections per year) Year 2+: Every other month (EOM, 6 injections per year)	Year 1: Every month (12 injections per year) Year 2+: Every other month (EOM, 6 injections per year)
Mean number of injections	14.80 [a]	24.99 [b]	24.99 [b]
Mean duration (months)	15.24 [a]	24.99	24.99
Cost per injection	$[redacted]	$[redacted]	$[redacted]
Cost/patient/year	$[redacted] (cost/patient/course over the trial duration of 18 months)	Year 1 (EM): $[redacted] Year 2+ (EOM): $[redacted]	Year 1 (EM): $[redacted] Year 2+ (EOM): $[redacted]

Source: Constructed during the evaluation from the
EM = Every month; EOM = Every other month.
[a] GATHER1 trial was conducted in two parts – Part 1 with N=25 patients and Part 2 with N=42 patients receiving 2mg ACP. Mean duration and mean number of injections for each part were weighted by the number of patients to estimate overall mean duration and mean number of injections used for patients receiving 2mg ACP in the GATHER1 trial.
[b] Mean number of injections were estimated by dividing total drug acquisition cost in the model with cost per injection

Estimated PBS usage & financial implications

6.72 This submission was not considered by DUSC. An epidemiological approach was used to estimate the extent of use and financial implications of listing ACP on the PBS. The key inputs utilised in the financial analysis are summarised in Table 17. The evaluation considered this was a reasonable approach given that there is currently no active comparator listed on the PBS. However, if pegcetacoplan is listed, market share calculations to all future projections of uptake and expenditure would be necessary.

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Australian population	ABS population projections, 2027-2032 (base year 2022) for individuals aged ≥ 50 years old.	The use of this data was reasonable noting that the proposed listing does not explicitly restrict access to ACP by age.
Incidence	0.17%, calculated from the cumulative 10-year incidence rate of 1.7% for GA reported in Wang et. al [24], applied to ABS population projections.	This was reasonable.
Prevalence	0.52%, weighted prevalence rate based on the prevalence rates reported for non-indigenous (aged ≥ 50 years old) and indigenous Australians (aged ≥ 40 years old) in Keel et. al [25]	Since the prevalence rates were applied to ABS population projections for individuals aged≥ 50 years old, it may have been more appropriate to utilise the prevalence rate that excluded indigenous Australians younger than 50 years of age to maintain consistency.
% of patients with non-sub foveal GA	31.60%, based on a retrospective analysis of patients in the IRIS registry with less than 24 months of follow-up data [26]	This was reasonable noting that the incidence of non-sub foveal GA in patients with over 24 months of follow up data was slightly lower (28.9%). The weighted proportion of patients with non-sub foveal GA for both cohorts was 30.01%.
Grandfathered patients	[redacted]1 patients accessing ACP privately, included in year 1 only	The submission assumed that all GF patients would receive PBS subsidised treatment for 24.99 months which was not reasonable as these patients should have initiated the ACP treatment privately.
% of patients electing treatment	[redacted]% in year 1, increasing to [redacted]% by year 6.	The low uptake rate in year 1 was not adequately justified in the submission. The PBAC considered the uptake rate at year 6 was overly optimistic. The PBAC considered uptake of [redacted]% in years 1 and 2 would be reasonable, increasing to [redacted]% by year 6.
Treatment duration	24.99 months, based on the modelled TTD.	This was reasonable.
ACP costs	$[redacted] per 2 mg vial, requested ex-manufacturer price	
Management of CNV events: Aflibercept and ranibizumab costs	$890.97 and $786.68, DPMAs of PBS items 13146X and 10138N	While the inclusion of these costs was appropriate, the submission included costs for 1 year only. However, CNV requires ongoing treatment and thus, the costs associated with management of CNV events was underestimated. The PSCR clarified that CNV costs are based on patient years of treatment rather than single year of treatment per patient. The

[24] Wang JJ, Rochtchina E, Lee AJ, Chia E-M, Smith W, Cumming RG, Mitchell P. Ten-year incidence and progression of age-related maculopathy: the blue Mountains Eye Study. Ophthalmology. 2007;114(1):92-8.

[25] Keel S, Xie J, Foreman J, Van Wijngaarden P, Taylor HR, Dirani M. Prevalence of age-related macular degeneration in Australia: the Australian National Eye Health Survey. JAMA ophthalmology. 2017;135(11):1242-9.

[26] Rahimy E, Khan MA, Ho AC, Hatfield M, Nguyen TH, Jones D, et al. Progression of geographic atrophy: retrospective analysis of patients from the IRIS® Registry (Intelligent Research in Sight). Ophthalmology Science. 2023;3(4):100318.

		mean annual number of aflibercept (7.0) and ranibizumab (8.8) injections was applied to patient-years of treatment. Patient-years were calculated by multiplying the number of patients by the average treatment duration of ACP treatment (2.08 years) used in the financial model. This corresponds to approximately 14.6 aflibercept injections and 18.3 ranibizumab injections per GA patient.
MBS costs	MBS item 43030 ($350.85), costs for intravitreal administration of ACP, applied per administration.	This was appropriate.

Source: tabulated during the evaluation, from Table 4.1-2, p220 of the submission and the "Attachment 14 – Izervay GA AMD Financial Model" workbook provided in the submission.
ABS = Australian Bureau of Statistics; ACP = avacincaptad pegol; GA = geographic atrophy; IRIS = Intelligent Research in Sight Registry; MBS = Medicare Benefits Schedule; mg = Milligram; PBS = Pharmaceutical Benefits Scheme; TTD = time-to-treatment discontinuation.
The redacted values correspond to the following ranges:
[1] < 500

6.73 The submission estimated the total number of patients eligible for treatment with ACP based on the inputs presented in Table 17. An incidence rate of 0.17% was applied to ABS population projections (2027-2032) for persons aged ≥ 50 years old. Prevalent patients were included in year 1 only. The number of prevalent patients was based on a weighted prevalence rate of 0.52% (weighted based on prevalence rates of 0.72% and 0.17% for indigenous and non-indigenous Australians) applied to Australian population projection for the year 2026. The weighted prevalence rate applied included indigenous Australians aged < 50 years old. Given that the ACP is proposed for patients aged 50 years old or more, this was not reasonable. The prevalence rate for non-indigenous Australians when patients aged < 50 years old are excluded was 0.26% (compared to 0.17%).

6.74 The submission assumed that 31.60% of patients with GA secondary to AMD would have non-sub foveal lesions. This was based on patients with less than 24 months of follow-up data in the IRIS registry. Of note, for patients with follow-up data of over 24 months, 28.9% of patients had non-sub foveal GA. The weighted proportion of patients with non-sub foveal GA for both cohorts (follow up of less than and more than 24 months) was 30.01%.

6.75 An uptake rate of [redacted]% in year 1, increasing to [redacted]% by year 6, were applied. The ESC considered the low uptake rate in year 1 was not adequately justified in the submission. < 500 grandfathered patients, who would access ACP privately, were included in year 1. The PBAC considered the uptake rate at year 6 was overly optimistic. The PBAC considered uptake of [redacted]% in years 1 and 2 would be reasonable, increasing to [redacted]% by year 6.

6.76 The total number of ACP prescriptions was based on the recommended treatment regimen of one dose per month in the first year (initial treatment) and one dose every other month thereafter (continuing treatment). As such, the submission estimated that patients would require 12 scripts per year for initial treatment and 6 scripts per year for continuing treatment. This does not allow for the possibility that some

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patients may continue to receive EM dosing after the first year, as suggested in the proposed listing and the PI. A mean treatment duration of 24.99 months (derived from the modelled TTD) was applied to all eligible patients that elect treatment. As outlined in paragraph 6.60, the PSCR argued that advice from clinicians and utilisation data from the United States of America supported use of EOM in the base case. The ESC considered that after the first 12 months of monthly ACP dosing a mixture of both EM and EOM dosing would likely occur in clinical practice. Consistent with the economic model, the ESC considered that it would be appropriate to model a 50:50 split of EM:EOM dosing after the first 12 months of EM treatment. The ESC noted that scenario 1 in Table 18 assumed 50% of patients would continue EM dosing of ACP after Year 1.

6.77 ACP was associated with an increase in CNV events compared to BSC in the GATHER 1 trial, i.e., 11.94% and 2.73% of patients had CNV events in the ACP and BSC arms, respectively. As such, the submission estimated an increase in aflibercept and ranibizumab scripts which are utilised to treat CNV events. Costs for one year of treatment were applied to 9.21% (11.94%-7.21%) of all eligible and treated patients. Patients may remain on treatment for longer than estimated in the submission. As a result, the costs associated with the management of CNV events may be underestimated in the base case analysis. The costs associated with aflibercept and ranibizumab prescriptions was estimated in the submission based on the DPMAs for each drug ($890.97 and $786.69, respectively).

6.78 Costs for the intravitreal administration of ACP was included per script using MBS item 43030 ($350.85). This was reasonable. The net financial implications of listing ACP is presented in Table 18. The evaluation identified the potential for ongoing monthly dosing allowed for the potential of significantly greater costs. Sensitivity analysis showing the impact of patients receiving EM dosing is also shown below.

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Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
ABS population (aged ≥ 50)	10,112,479	10,290,885	10,472,211	10,654,919	10,848,881	10,112,479
Estimated extent of use of ACP						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patient-years on treatment [a]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of scripts dispensed [b]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][6]	[redacted][6]
Estimated financial implications of ACP						
Cost to PBS/RPBS less copayments [c]	$[redacted][7]	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][10]
Estimated financial implications for aflibercept and ranibizumab						
Number of scripts dispensed [d]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost to PBS/RPBS less copayments [e]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]	$[redacted][11]
Net financial implications [adapt as required, present net costs to MBS, public hospitals and/or Australian government health budget if they are presented in the submission]						
Net cost to PBS/RPBS	$[redacted][7]	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][10]	$[redacted][10]
Net cost to MBS [f]	$[redacted][11]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]	$[redacted][12]
Net cost to PBS/RPBS/MBS	**$[redacted][13]**	**$[redacted][9]**	**$[redacted][10]**	**$[redacted][14]**	**$[redacted][14]**	**$[redacted][15]**
Scenario analyses						
Scenario 1: 50% of patients continue EM dosing after year 1						
Net cost to the PBS/RPBS	$[redacted][7]	$[redacted][8]	$[redacted][10]	$[redacted][10]	$[redacted][14]	$[redacted][14]
Scenario 2: 100% of patients continue EM dosing after year 1						
Net cost to the PBS/RPBS	$[redacted][7]	$[redacted][9]	$[redacted][10]	$[redacted][14]	$[redacted][15]	$[redacted][15]

Source: tabulated during the evaluation, from the "Attachment 14 – Izervay GA AMD Financial Model" workbook provided in the submission.
ABS = Australian Bureau of Statistics; ACP = avacincaptad pegol; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

[a] Based on a mean treatment duration of 24.99 months.

[b] Assuming 12 scripts/year for initial treatment and 6 scripts/year for continuing treatment.

[c] Based on a DPMA of $[redacted] per script (AEMP of $[redacted] per vial).

[d] Based on 7 scripts for aflibercept and 8 scripts for ranibizumab.

[e] Based on DPMAs of $890.97 and $786.69, applied to 9.21% of patients (patients with CNV events in GATHER 1).

[f] Based on MBS item 43030 ($350.85, 80% benefit) applied to each ACP script.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*
[2] *5,000 to < 10,000*
[3] *20,000 to < 30,000*
[4] *40,000 to < 50,000*
[5] *50,000 to < 60,000*
[6] *60,000 to < 70,000*
[7] *$20 million to < $30 million*
[8] *$40 million to < $50 million*
[9] *$50 million to < $60 million*
[10] *$60 million to < $70 million*
[11] *$0 to < $10 million*
[12] *$10 million to < $20 million*
[13] *$30 million to < $40 million*
[14] *$70 million to < $80 million*
[15] *$80 million to < $90 million*

6.79 The submission estimated a cost of $20 million to < $30 million in year 1, increasing to $60 million to < $70 million in year 6 and a cumulative cost of $300 million to < $400 million over the first 6 years of listing. As noted previously, the submission assumed that all patients would be treated with ACP EOM after the first year which the ESC considered was not reasonable as the listing allows for EM/EOM dosing after year 1.

Overall, the ESC agreed with the evaluation that the net costs to the PBS/RPBS have been underestimated in the submission. The ESC considered it more appropriate to anticipate that 50% of patients would likely continue to use EM dosing of ACP after 1 year. The ESC noted that while the estimated cost to the PBS/RPBS remained the same in year 1 ($20 million to < $30 million), the estimated cost increased to $70 million to < $80 million in year 6 with a cumulative cost of $300 million to < $400 million over the first 6 years of listing.

Quality Use of Medicines

6.80 The sponsor stated that comprehensive education materials that provide detailed information on the appropriate use of ACP, peer-to-peer education programs and a safety management program (including routine pharmacovigilance activities, real-word evidence collection, up-to-date consumer medicines information and a risk management plan) would be developed if ACP is listed on the PBS. No other QUM issues were identified.

Financial Management – Risk Sharing Arrangements

6.81 The ESC noted that the submission did not propose a risk sharing arrangement. The ESC considered that such an arrangement may be required to address any residual uncertainty around the patient numbers and the proportion of patients likely to receive EM or EOM dosing of ACP.

6.82 In its recommendation for pegcetacoplan, the PBAC considered that a risk sharing arrangement was required, including to address any residual uncertainty regarding estimated patient numbers and ensure PBS reimbursement was for treatment in one eye only (paragraph 7.17, pegcetacoplan PSD, November 2025 PBAC meeting).

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of avacincaptad pegol (ACP), 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 ACP 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 will result in better functional vision. The PBAC considered more conservative assumptions for the model would help address the uncertainty of transforming slower lesion growth to a reduction in vision loss. 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 $45,000 to < $55,000 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 (RSA) 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 it had previously recommended pegcetacoplan for this condition at its November 2025 meeting, however the listing had not yet progressed at the time of its consideration of ACP. The PBAC considered that it does not appear that one agent is clearly superior to the other at slowing lesion growth. Should pegcetacoplan proceed to PBS listing, the PBAC advised that a cost-minimisation approach (accounting for differences in administration costs) was appropriate to ensure that ACP was no more costly than pegcetacoplan. Equi-effective doses over 2 years were:

- ACP 2 mg once monthly intravitreal (IVT) injection (single eye) for the first 12 months, followed by 2 mg IVT injection every other month (18 injections); and
- pegcetacoplan 15 mg IVT injection (single eye) once every other month (12 injections).

7.3 The PBAC noted the support from Macular Disease Foundation Australia 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. The PBAC also noted mixed support from health care professionals, with some noting delayed retinal degeneration would offer meaningful benefit by helping patients retain their sight for longer, with others suggesting the evidentiary basis for PBS listing was limited and such mild/small delays in anatomical progression of GA were insufficient to translate into meaningful outcomes for patients.

7.4 The PBAC noted the discrepancy in support for ACP, but also that there was a high clinical need for treatments to prevent vision loss in patients with GA secondary to AMD. The PBAC noted in its recommendation for pegcetacoplan in November 2025, the proposed population was for treatment of patients who had already experienced vision loss in one eye, as these were considered the highest priority patients and it had agreed with the Advisory Committee on Medicines (ACM) 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 (paragraph 7.3, pegcetacoplan PSD, November 2025 PBAC meeting). As ACP evidence for safety and efficacy is similarly aligned with pegcetacoplan, the PBAC considered ACP should be made available on the PBS only under the same circumstances.

7.5 The PBAC considered the PBS restriction for ACP should align with that recommended for pegcetacoplan in November 2025. However, the PBAC noted the pre-PBAC response arguments against the ESC's suggested requirement of specifying an

anatomical distance for the lesion from the foveal centre, or imaging indicating lesion growth progression towards the foveal centre (see paragraph 3.3). The PBAC agreed that the intent was to identify high risk patients, rather than specify a numerical threshold and, as such, the PBAC recommended that the restriction wording would be sufficient if it specified that the patient must have an intact fovea and that a patient's central vision is threatened by GA lesion growth — the following wording could be used: 'The patient must have non-subfoveal geographic atrophy (GA) lesions(s) in the treated eye' and 'Patient must have central vision in the treated eye threatened by growth of GA lesion(s), either due to proximity to the foveal centre or where historical imaging shows lesion progression towards the foveal centre and is located within the macula'. This would allow clinical discretion to determine if a patient could potentially benefit from treatment. The PBAC noted that this differs from the recommended pegcetacoplan restriction (see section 8, pegcetacoplan PSD, November 2025 PBAC meeting), and that it would be appropriate to flow-on this change to the pegcetacoplan restriction as outlined in paragraph 8.3.

7.6 The PBAC further advised that no exclusion of concomitant CNV therapy is required, and that concomitant treatment with CNV can be left to clinician discretion. The PBAC advised that, should pegcetacoplan proceed to listing, no concomitant or sequential therapy with pegcetacoplan for GA secondary to AMD should be allowed given the similar mechanisms of action and the absence of clinical efficacy or safety data of concomitant or sequential use (see paragraph 8.2 and 8.4). The PBAC considered that the requested grandfathering restriction for patients in the sponsor's patient access program would not be required as patients that would not meet the proposed PBS restriction eligibility criteria should not be eligible for PBS subsidy for ACP.

7.7 The PBAC accepted the nominated comparator of BSC was appropriate. The PBAC accepted pegcetacoplan was an appropriate near market comparator.

7.8 The PBAC noted the submission was based on 2 randomised Sham-controlled trials: GATHER1 (Phase 2/3) and GATHER2 (Phase 3). In Part 1 of GATHER1, patients were randomised to receive ACP 1 mg IVT, ACP 2 mg IVT, or Sham. In Part 2 of GATHER1, patients were randomised to receive ACP 2 mg IVT, ACP 4 mg IVT, or Sham. In GATHER1, there were 67 patients in the combined ACP 2 mg group (N = 67) and 110 patients in the combined Sham group (N = 110). In GATHER2, patients were randomised at baseline to receive either monthly ACP 2 mg IVT (N = 225) or Sham (N = 222). At Month 12, after the collection of data for the primary endpoint analyses, patients who had previously received monthly ACP 2 mg IVT were re-randomised to receive either ACP 2 mg monthly (EM) (N = 96) or ACP 2 mg every other month (EOM) (N =93).

7.9 The PBAC noted the outcomes of observed mean rate of change in GA area and mean rate of change in GA growth were significantly improved with ACP treatment compared to Sham injection, over 12, 18 and 24 month timepoints (see Table 4 and Table 5). The PBAC noted that the claim of similar efficacy for EOM to EM IVT is based on indirect inference rather than rigorous statistical evidence (paragraph 6.19).

However, the PBAC was satisfied that there were no substantial differences in outcomes for patients receiving EM or EOM dosing, although it was noted the patient numbers were small.

7.10 The PBAC noted there were no significant benefits in the secondary efficacy endpoints of BCVA and low luminance-BCVA (LL-BCVA]) (ETDRS letters) (see Table 6). The PBAC noted that, based on the TGA Delegate's overview, GA area has emerged as an appropriate variable to assess progression of GA, in particular in the earlier stages of the disease, since visual acuity would poorly reflect GA progression if the fovea remains unaffected (see paragraph 6.12). The PBAC recalled from its November 2025 consideration of pegcetacoplan that, although the clinical trials did not demonstrate clear improvements in vision related activities, it had considered it was reasonable to assume that protecting the structure of the eye by slowing GA lesion growth would likely result in slower loss of functional vision than current care. Despite uncertainty in the magnitude of this benefit on vision, in November 2025, the PBAC was satisfied that pegcetacoplan provides, for some patients, a significant improvement in efficacy over BSC (Pegcetacoplan, November 2025 PBAC Meeting outcomes). The PBAC considered that for ACP, the claim of superior effectiveness to BSC was adequately supported but the magnitude of benefit was uncertain.

7.11 The PBAC noted that combining data from GATHER1 and GATHER2, ACP 2 mg IVT appeared to have a stronger association with the development of CNV in the treated eye during the first 12 months of treatment. The PBAC also noted that data from the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS) Registry reported a lower percentage of patients developing CNV than reported in the clinical trials. The PBAC noted among the adverse events of special interests (AESIs) in GATHER2, patients in the ACP group experienced 6 times higher rate of IOP ≥ 30 mmHg (12.4% in ACP vs 1.8% in Sham) and a higher rate of increased IOP requiring surgery (4.4% in ACP vs 0 in Sham), and 3 times higher rate of decreased/blurred vision (15.1% in ACP vs 5.0% in Sham). Overall, the PBAC considered the claim of inferior safety to BSC was appropriate.

7.12 The PBAC noted no head-to-head trials directly compared the efficacy and safety of ACP versus pegcetacoplan in the proposed target population, and therefore the submission presented three indirect treatment comparisons (ITCs): an anchored matching-adjusted indirect comparison (MAIC)[27] (the Sham arm was an anchor), an ITC using network meta-analysis (NMA)[28], and an ITC using multi-level network

[27] Hahn P, Eichenbaum D, Dhoot D et al. Efficacy of intravitreal pegcetacoplan vs avacincaptad pegol in patients with geographic atrophy. *J Vitreoretin Dis* 2025. DOI 10.1177/24741264251379842

[28] Wang H, Zheng J, Zhang Q et al. Efficacy and safety of complement inhibitors in patients with geographic atrophy associated with age-related macular degeneration: a network meta-analysis of randomized controlled trials. *Front Pharmacol* 2024; 15:1410172.

meta-regression (ML-NMR)[29]. The MAIC was informed by GATHER2, and the DERBY and OAKS pegcetacoplan trials; the ML-NMR was informed by GATHER1 and GATHER2, and DERBY, OAKS, and FILLY. The NMR included ten RCTs and five complement inhibitors (ACP [C3i], pegcetacoplan [C5i], lampalizumab [Factor D], CLG561 [C3i and C5i], and LFG316 [C5i]) for analyses.

7.13 The PBAC noted the transitivity issues with the ITCs and the limitations of the MAIC (see paragraph 6.24). The PBAC noted the ESC reviewed the novel use of the ML-NMR (see paragraph 6.25). The PBAC agreed with the ESC that, as outlined in paragraph 6.26, while the overall interpretation of the comparison between ACP and pegcetacoplan based on the ML-NMR remained challenging, it does not appear that one agent is clearly superior to the other, and the claim of non-inferior comparative effectiveness to pegcetacoplan was reasonable.

7.14 The submission described ACP as non-inferior to pegcetacoplan in terms of safety. The PBAC noted the key issue was that there was a fundamental difference in terms of the risk of new onset CNV in treated eye at baseline between the ACP trial population and the pegcetacoplan trial population which could not be adjusted for in the indirect comparison. The PSCR clarified that the ML-NMR compared risks for ACP with the pegcetacoplan patients in whom CNV was absent at baseline. Overall, the PBAC agreed with the ESC that a claim of non-inferior safety was uncertain but likely reasonable.

7.15 The PBAC noted the submission presented a modelled economic evaluation based on the direct randomised trials, GATHER1 and GATHER2. The economic model relied on the progression of vision loss classified by health states differentiated based on GA area (small, medium, large, blind) and minimum distance to the foveal centre (close or far). These states are proxies for disease severity and risk of vision loss. The PBAC noted the ESC had advised that the translation of these clinical measures into functional and directly patient relevant outcomes required additional assumptions and outcome translations that, while reasonable in principle (as indicated by the PBAC in their consideration for pegcetacoplan), are associated with considerable uncertainty.

7.16 The PBAC noted the ESC requested a multivariate analysis (see paragraph 6.70 and Table 15) to address its key concerns and offer an alternative base case. The PBAC agreed with the following alternative parameters to inform the base case ICER: reduce the time horizon from 20-years to 15-years; remove the application of excess mortality from the severe visual impairment health states; pool the data from GATHER1 and GATHER2; and apply a utility decrement for ACP administration. The PBAC noted that the PSCR and pre-PBAC response had emphasised the utilisation data from the United

[29] Jovanović J, Daki V, Kantidakis G et al. (2025) Comparative efficacy and safety of avacincaptad pegol vs pegcetacoplan in treatment of geographic atrophy: insights from a multilevel network meta-regression (Conference paper).

States of America (August 2023 to November 2025) and support from clinicians that EOM dosing was preferred to EM (see paragraph 6.60). The PBAC was satisfied that the frequency of administration in the submission base case was likely appropriate, with EOM dosing from year 2 onwards, rather than the 50:50 split between EM and EOM as proposed by the ESC. The PBAC noted the revised base case ICER with its preferred parameters would be $75,000 to < $95,000 (see paragraph 6.71 and Table 15). The PBAC considered with these alternative parameters the cost-effectiveness analysis would be more reliable. The PBAC noted that in the ACP economic model progression of vision loss was modelled based on GA area and minimum distance to the foveal centre, whereas in the pegcetacoplan model progression was modelled based on Early Treatment Diabetic Retinopathy study (ETDRS) letters. While it was not possible to directly compare the models the PBAC considered the larger QALY gain estimated from the ACP model compared with the pegcetacoplan model was inconsistent with the conclusion of non-inferior efficacy and safety. In this context the PBAC considered an ICER in the order of $45,000 to < $55,000 per QALY gained would be acceptable. The PBAC noted that a price reduction would be required to achieve cost effectiveness.

7.17 The PBAC noted that an epidemiological approach was used to estimate the extent of use and financial implications of listing ACP on the PBS, which was reasonable. The PBAC considered the uptake rates proposed by the submission were uncertain, particularly with the possibility of some hesitation due to the effective monocular vision status of the target population. However, the PBAC noted that there are no other subsidised treatment options available for GA. 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 increasing only up to [redacted]% by year 6. The PBAC considered that patient numbers would need to be updated to reflect patients with bilateral GA and the proportion with non-subfoveal GA in one eye and subfoveal GA in the fellow eye. The PBAC advised these rates should align with the pegcetacoplan consideration in November 2025 (Table 15, pegcetacoplan PSD, November 2025 PBAC meeting).

7.18 The PBAC noted that the PBS listing of ACP would pose high financial risk to Government for uncertain functional benefits. To ensure use remains within acceptable cost-effectiveness parameters, the PBAC considered an RSA was appropriate. The PBAC considered the RSA would specifically address uncertainty in the prevalence of monocular patients and the uptake rates. The PBAC recommended an [redacted]% rebate for expenditure above the RSA caps. Should the pegcetacoplan PBS listing be finalised ahead of ACP, it would be appropriate for ACP to join the same RSA as pegcetacoplan, with no increase in the caps.

7.19 The PBAC recommended that avacincaptad pegol should not be treated as interchangeable with any other drugs.

7.20 The PBAC advised that avacincaptad pegol is not suitable for prescribing by nurse practitioners. The PBAC also recommended that avacincaptad pegol 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.

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

7.22 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 avacincaptad pegol:

a) The treatment is expected to provide a clinically relevant improvement in efficacy over standard care for slower GA lesion growth, 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.

7.23 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**
AVACINCAPTAD PEGOL					
avacincaptad pegol 8.68 mg (equivalent to oligonucleotide 2 mg)/0.1 mL intraocular injection, 0.1 mL vial	NEW	1	1	5	Izervay
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	**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) in the eye intending to be treated
		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 eye intending to be treated threatened by growth of GA lesion(s), either due to proximity to the foveal centre or where historical imaging shows lesion progression towards the foveal centre and is located within the macula
		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
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.
Prescribing rule level	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
Prescribing rule level	**Administrative Advice:** Special Pricing Arrangements apply.
	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) in the treated eye
	Treatment criteria:
	Must be treated by an ophthalmologist or by an accredited ophthalmology registrar in consultation with an ophthalmologist.

	Prescribing Instructions: At the time of the authority application, medical practitioners should request the appropriate number of repeats to provide for a continuing course of this drug sufficient for up to 24 weeks of therapy.
	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).

8.2 Flow on changes to ACP listing should pegcetacoplan be listed for this indication: Amend Initial treatment and Continuing treatment listings for ACP with the addition of the following clinical criteria:

Initial treatment:

Add new concept IDs:

New CC	***Clinical criteria:***
	Patient must not have previously received treatment with pegcetacoplan for this condition prior to initiating PBS-subsidised treatment with this drug
	AND
	Clinical criteria:
	Patient must not be receiving concomitant treatment with pegcetacoplan for this condition

Continuing treatment:

Add new concept IDs:

New CC	***Clinical criteria:***
	Patient must not be receiving concomitant treatment with pegcetacoplan for this condition

8.3 Flow on changes to pegcetacoplan listing should pegcetacoplan be listed for this indication:

Amend the Initial treatment and Continuing treatment listings outlined in Section 8, pegcetacoplan PSD, November 2025 PBAC meeting as follows in order to remove numerical values associated with confirmation of lesion growth and location:

Initial treatment:
Amend concept IDs:

New CC	**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 ~~-~~*intending to be treated*
	AND
New CC	**Clinical criteria:**
	Patient must have central vision in the ~~treated~~ eye *intending to be treated* threatened by growth of GA lesion(s), *either due to proximity to the foveal centre or where historical imaging shows lesion progression towards the foveal centre and is located within the macula* ~~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).~~

Continuing treatment:

Amend concept IDs:

New CC	**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

8.4 Flow on changes to pegcetacoplan listing should ***both*** pegcetacoplan and ACP be listed for this indication:

Amend the Initial treatment and Continuing treatment listings for pegcetacoplan outlined in Section 8, pegcetacoplan PSD, November 2025 PBAC meeting as follows to add new concept ID excluding sequential and concomitant therapy with ACP:

Initial treatment:

Add new concept IDs:

New CC	***Clinical criteria:***
	Patient must not have previously received treatment with avacincaptad pegol for this condition prior to initiating PBS-subsidised treatment with this drug
	AND
	Clinical criteria:
	Patient must not be receiving concomitant treatment with avacincaptad pegol for this condition

Continuing treatment:

Add new concept IDs:

New CC	***Clinical criteria:***
	Patient must not be receiving concomitant treatment with avacincaptad pegol for this condition

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

Astellas Pharma Australia thanks PBAC for the recommendation and looks forward to coming to a commercially agreeable and evidence-based arrangement - in order to PBS List.