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Comparative efficacy and safety of avacincaptad pegol vs pegcetacoplan in treatment of geographic atrophy: insights from a multilevel network meta-regression

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INTRODUCTION

- Avacincaptad pegol (ACP), a pegylated complement C5 inhibitor aptamer, and pegcetacoplan (PEG), a pegylated complement C3 inhibitor peptide, are intravitreal complement inhibitors approved by the US Food and Drug Administration (FDA) for slowing the progression of GA secondary to AMD[1,2]
- ACP and PEG have not been directly compared in a randomized controlled trial (RCT)
- The inference on the relative efficacy of ACP and PEG from a previous matching-adjusted indirect comparison (MAIC)[3] are limited due to:
  - Potential selection and reporting bias (exclusion of functional and safety outcomes, and of GATHER1 data)
  - Inappropriate methodology
  - Poor population overlap between ACP and PEG trials, which led to particularly low effective sample size, and disproportionate impact of a few individuals on the relative effects

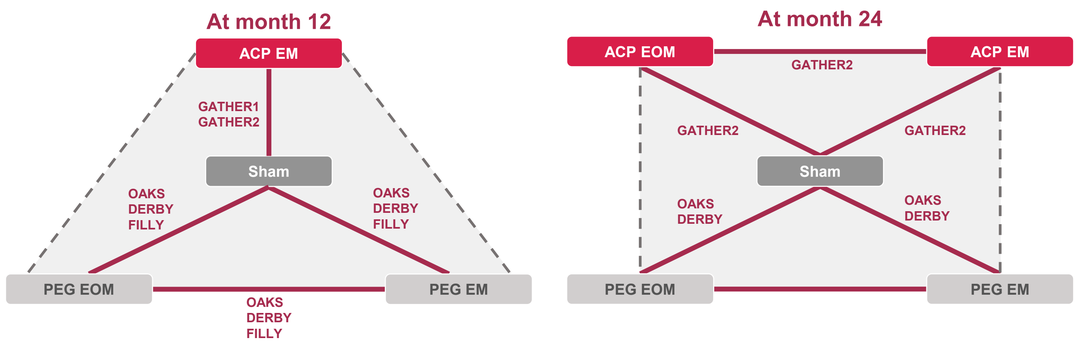
OBJECTIVE

- To evaluate the efficacy and safety of ACP relative to PEG for the treatment of GA using multilevel network meta-regression (ML-NMR) methodology, which is the recommended method when population overlap is limited

METHODS

- A systematic literature review (SLR) was conducted via Ovid databases (Embase®, MEDLINE®, CDSR, CENTRAL) and supplementary sources (searches performed on December 7, 2023)
  - Only RCTs of ACP[4,5] and PEG[6,7] were included in the indirect treatment comparison (ITC) evidence base. Other interventions not licensed in GA or in early-phase development lacking published results at the time of the SLR were excluded
  - Identified studies formed a connected evidence network with sham as a common comparator (**Figure 1**)

Figure 1. General networks of evidence at month 12 and month 24



GATHER1 and FILLY were not included in the 24-month analysis due to their shorter durations of 18 and 12 months, respectively.

- ML-NMR combined individual patient-level data (IPD) from ACP trials with aggregate data from PEG trials, adjusting for population differences
  - Both fixed- and random-effects models were tested; model selection was based on Deviance Information Criterion (DIC) and Watanabe-Akaike Information Criterion (WAIC)
  - Key effect modifiers were identified through a literature review and expert consultations. Age and choroidal neovascularization (CNV) in the fellow eye were identified as key risk factors for adverse events in the study eye
  - The shared effect modifier assumption was applied in all analyses
- Outcomes assessed in the ACP and PEG RCTs (5 trials in total) are shown in **Table 1**
- Analyses were performed in a Bayesian framework using Stan (R "multinma" package)[8]
  - Missing baseline covariates were imputed using the missForest algorithm
  - Statistical significance was defined as 95% credible interval (CrI) not crossing 0 (median difference) or 1 (median odds ratio)

Table 1. RCTs included in the evidence base and outcomes reported per study timepoint

Outcome per study timepoint	Month 12		Month 24		Effect modifiers adjusted in the ML-NMR
Mean change from baseline in GA lesion size	GATHER1/ GATHER2	OAKS / DERBY / FILLY	GATHER2	OAKS / DERBY	Minimum distance to foveal center (≤0.25 mm or >0.25 mm)*; baseline GA lesion area; low-luminance deficit; lesion laterality; lesion focality; age; gender
Mean change from baseline in best-corrected visual acuity (BCVA)†	GATHER1/ GATHER2	OAKS & DERBY combined / FILLY	GATHER2	OAKS & DERBY combined	
Mean change from baseline in low luminance BCVA (LL-BCVA)‡	GATHER1/ GATHER2	FILLY	GATHER2		
Mean change from baseline in Visual Function Questionnaire 25 (VFQ-25) distance activity score	GATHER1/ GATHER2		GATHER2	OAKS & DERBY combined	Age; gender; BCVA (study eye); LL-BCVA (study eye); lesion laterality
Incidence of ocular treatment-emergent adverse events (TEAEs), serious ocular TEAEs	GATHER1/ GATHER2	OAKS / DERBY / FILLY	GATHER2	OAKS / DERBY	Age
Incidence of new onset CNV in the study eye			GATHER2	OAKS & DERBY combined§ / FILLY¶	Age

ACP RCTs
PEG RCTs

*Used as a proxy for centerpoint involvement in GATHER trials. †ML-NMR of BCVA included GA lesion growth rate quartiles, defined per OAKS and DERBY, as an additional effect modifier. data available only at month 24. ‡The distance from fovea was not included in the ML-NMR of LL-BCVA as it was unavailable in FILLY. §Subgroup of participants without fellow eye CNV at baseline. ¶Safety data for the FILLY study reflect the full follow-up period from study drug initiation to month 18.

STRENGTHS AND LIMITATIONS

- The **key strength** of this analysis is the use of ML-NMR, which leverages all available data to achieve robust population adjustment across all effect modifiers identified through published evidence and/or clinical opinion
- Interpretation of the results may be limited by:
  - The use of a proxy for foveal centerpoint lesions for the ACP trials due to missing baseline and outcome data for the extra-subfoveal subgroup in OAKS and DERBY
  - Furthermore, the ML-NMR's inability to handle longitudinal data may also limit the interpretation of the results
- As with any population-adjustment method for ITC, there is a possibility of residual bias in the results of the ML-NMR due to unobserved or unreported effect modifiers

Abbreviations: ACP, avacincaptad pegol; AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; CrI, credible interval; DIC, Deviance Information Criterion; EM, every month; EOM, every other month; ETDRS, Early Treatment Diabetic Retinopathy Study; FDA, US Food and Drug Administration; GA, geographic atrophy; IPD, individual patient-level data; ITC, indirect treatment comparison; LL, low luminance; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; PEG, pegcetacoplan; RCT, randomized controlled trial; SLR, systematic literature review; TEAE, treatment-emergent adverse event; VFQ-25, Visual Function Questionnaire 25; WAIC, Watanabe-Akaike Information Criterion.

References: 1. Izervay. Package insert. Astellas Pharma, Inc.; 2024. **2.** Syfovre. Package insert. Apellis Pharmaceuticals, Inc.; 2024. **3.** Hahn P, et al. *J Vitreoretin Dis*. 2025;17:24741264251379842 [Epub ahead of print]. **4.** Jaffe GJ, et al. *Ophthalmology*. 2021;128(4):576–586. **5.** Khanani AM, et al. *Lancet.* 2023;402(10411):1449–1458. **6.** Liao DS, et al. *Ophthalmology.* 2020;127(2):186–195. **7.** Heier JS, et al. *Lancet*. 2023;402(10411):1434–1448. **8.** Phillippo DM (2024). multinma: Bayesian network meta-analysis of individual and aggregate data. doi:10.5281/zenodo.3904454, R package version 0.8.1, https://dmphillippo.github.io/multinma/. **9.** Phillippo DM, et al. *J R Stat Soc Ser A Stat Soc.* 2020;183(3): 1189–1210. **10.** Guo JD, et al. *BMJ Open*. 2025;15(3):e091961.

RESULTS

- A total of 40 publications describing 28 clinical trials reporting efficacy endpoints of treatments for GA were retrieved; only the 2 currently FDA-approved treatments[1,2] were included in the analysis

Efficacy

GA lesion size

- At month 12, ACP showed similar efficacy in reducing change from baseline in GA lesion size as PEG every month (EM)/every other month (EOM) (**Figure 2A**). A comparable trend was seen at month 24 (**Figure 2B**)

BCVA

- At month 12, ACP showed a similar efficacy in attenuating the loss of BCVA as PEG EM or PEG EOM (+1.07 and +2.36 Early Treatment Diabetic Retinopathy Study [ETDRS] letters, respectively). The relative effect of ACP versus PEG was similar at month 24

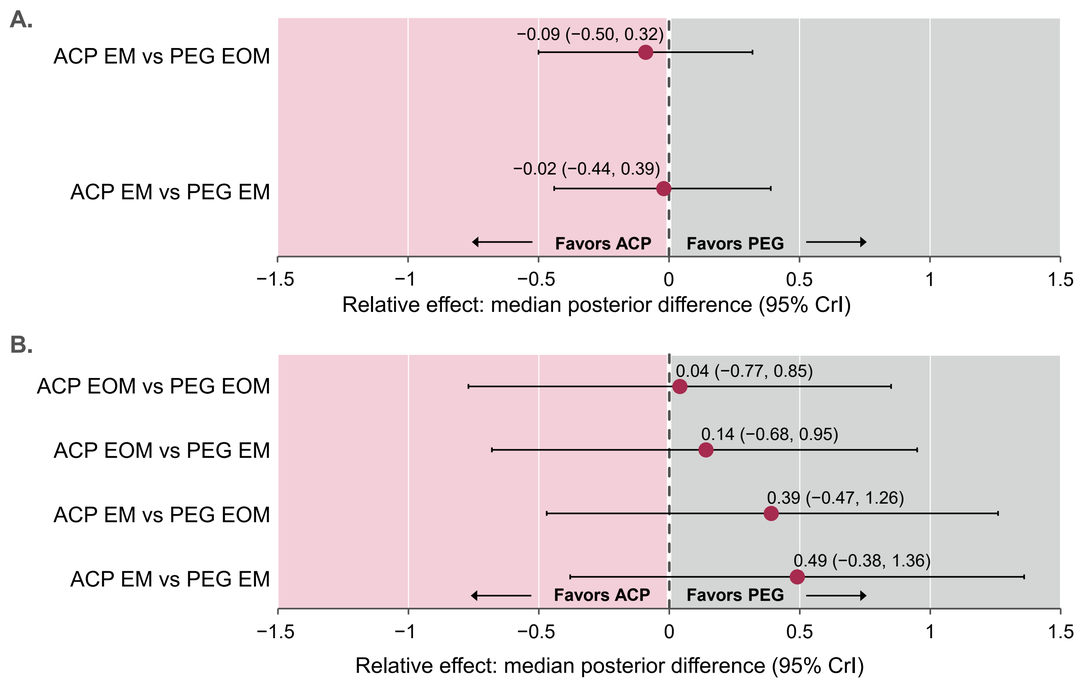
LL-BCVA

- At month 12, ACP showed similar efficacy in attenuating the loss of LL-BCVA relative to PEG EM or PEG EOM (+0.19 and +0.79 ETDRS letters, respectively)
- Analysis at month 24 was precluded by the lack of outcome data in PEG studies

VFQ-25

- At month 24, minor differences between ACP and PEG were neither statistically nor clinically significant due to the wide 95% CrI (~17 points), limiting the interpretability of the results

Figure 2. Relative effect of ACP vs PEG for the change from baseline in GA lesion size at month 12 (A) and at month 24 (B)

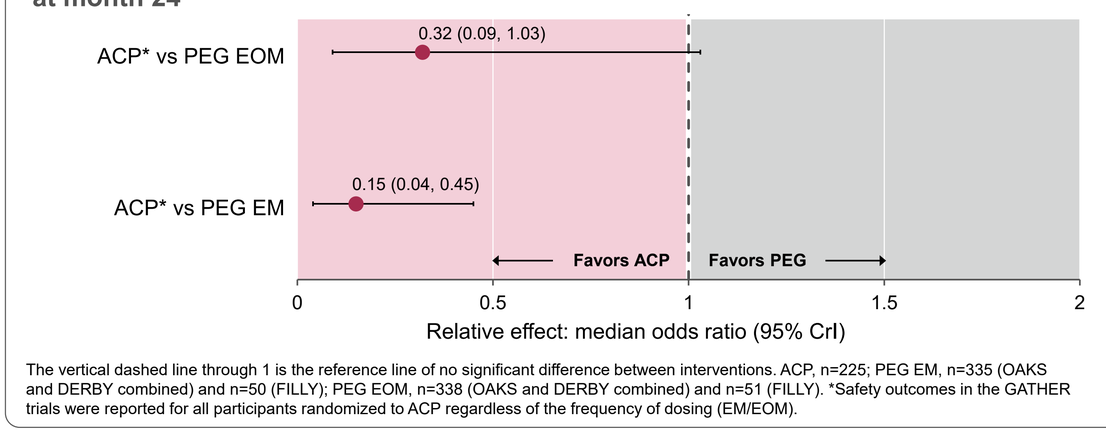


The vertical dashed line through 0 is the reference line of no significant difference between interventions. During the first 12 months, ACP was administered EM. The EOM dosing was introduced after re-randomization at month 12.
Panel A: ACP, n=50 (GATHER1) and n=175 (GATHER2); PEG EM, n=159 (OAKS), n=150 (DERBY), and n=84 (FILLY); PEG EOM, n=165 (OAKS), n=163 (DERBY), and n=78 (FILLY). *Panel B:* ACP EM, n=81; ACP EOM, n=73; PEG EM, n=134 (OAKS) and n=139 (DERBY); PEG EOM, n=162 (OAKS) and n=154 (DERBY).

Safety

- **At month 24, the odds of experiencing new onset CNV in the study eye were lower in participants treated with ACP versus those treated with PEG EM by 85%, a difference that is both statistically and clinically meaningful (Figure 3)**
  - The relative effect of ACP versus PEG EOM on the odds of new onset CNV was similar

Figure 3. Relative effect of ACP vs PEG for the risk of experiencing new onset CNV at month 24



The vertical dashed line through 1 is the reference line of no significant difference between interventions. ACP, n=225; PEG EM, n=335 (OAKS and DERBY combined) and n=50 (FILLY); PEG EOM, n=338 (OAKS and DERBY combined) and n=51 (FILLY). *Safety outcomes in the GATHER trials were reported for all participants randomized to ACP regardless of the frequency of dosing (EM/EOM).

CONCLUSIONS

- This analysis helps address a critical evidence gap in the evolving treatment paradigm for GA. Due to the shared effect modifier assumption, the relative effects reported are applicable to any population in the evidence base
- To our knowledge, this is the first robust indirect comparison of ACP and PEG to assess their relative efficacy and safety
  - In contrast to MAIC, which can only compare 2 RCTs at a time, ML-NMR integrates evidence across multiple connected studies and treatments[9,10]
  - Unlike MAIC, which is a weighting-based method, ML-NMR is a regression-based method, which allows to derive relative effects for any population in the evidence base
- **In this analysis, ACP was associated with a significantly lower odds of new onset CNV relative to PEG while maintaining similar efficacy in slowing GA lesion growth and visual acuity loss**

Disclosures: Jelena Jovanović, Vagia Daki, Georgios Kantidakis, and Ines Guerra are employees of IQVIA and were contracted by Astellas for conducting work related to this publication. Scott Doyle, Maria Mata Lorenzo, and He Guo are employees of Astellas.

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Disclaimer: Avacincaptad pegol (ACP) received US FDA approval for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) on August 4, 2023. ACP received conditional approval for the suppression of GA growth in atrophic AMD in Japan on September 19, 2025. In Australia, ACP received approval for the treatment of adult patients with GA secondary to AMD with an intact fovea and when central vision is threatened by GA lesion growth on October 13, 2025.

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