7/30/2023 12:00 am

Dry AMD Symposium 2

Treatment of Geographic Atrophy Secondary to Age-Related Macular Degeneration With Intravitreal ANX007: Results of the ARCHER Study

- Jeffrey Heier, MD
- Charles Wykoff, MD, PhD, FASRS
- Glenn Jaffe, MD
- Allen Hu, MD
- David Lally, MD
- Roger Goldberg, MD, MBA
- Carl Regillo, MD
- David Boyer, MD
- Karl Csaky, MD, PhD
- Wendy Murahashi
- Harman Hansra
- Lori Taylor, PhD
- Donald Fong, MD, MPH

Objective: To assess the efficacy and safety of intravitreal ANX007, a novel antibody fragment targeting C1q, in the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).
Purpose: ANX007, an antigen-binding fragment (Fab), binds to C1q, inhibiting activation of the classical complement pathway. ARCHER is a randomized, double-masked, sham-controlled study of the efficacy, safety and tolerability of ANX007 in patients with geographic atrophy (GA). The ARCHER primary endpoint is comparison of the rate of change (slope) in GA lesion growth at 12 months between ANX007 and sham.
Methods: Patients were randomized 2:2:1:1 to 5 mg intravitreal (IVT) ANX007 monthly (MO) or every other month (EOM), sham MO, or sham EOM during the 12-month treatment period and were followed off-treatment for 6 additional months. Well de-marcated foveal and non-foveal lesions (total lesion area ≥ 2.5 mm^2 and ≤ 17.5 mm^2 and at least one leasion with area ≥ 1.5 mm^2 if lesions where multi-focal) were eligible. A best-corrected visual acuity (BCVA) of 24 to 83 letters using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (20/25 to 20/320 Snellen equivalent) was required. A history or presence of choroidal neovascularization (CNV) and CNV treatment in the fellow eye was permitted.
Results: Approximately 270 patients were enrolled from February 2021 through March 2022. The average patient age was 78 (MO) and 80 (EOM) years, of which 58% (MO) and 65% (EOM) were women. Approximately 45% of all patients had non-foveal lesions. The primary efficacy analysis is the rate of change (slope) from baseline to Month 12 in GA lesion area, as assessed by fundus autofluorescence (FAF) imaging. The secondary analysis includes the change from baseline to Month 12 in GA lesion area, as assessed by FAF imaging, the change from baseline to Month 12 in BCVA, the change from baseline to Month 12 in low-luminance BCVA (LL-BCVA) and the change from baseline to Month 12 in low-luminance visual acuity deficit (LL-VD). The incidence and severity of ocular and systemic treatment-emergent adverse events (AEs) are also evaluated. The first reporting of results of the primary analysis at Month 12 will be presented.
Conclusion: C1q, the initiating molecule of the classical complement pathway, has been implicated in neurodegenerative diseases, including GA. ANX007 is designed to inhibit C1q while allowing immune functions of the lectin and alternative complement pathways to continue. The primary efficacy and selected secondary efficacy and safety and tolerability results for the ARCHER study will be presented.

IRB APPROVAL Yes

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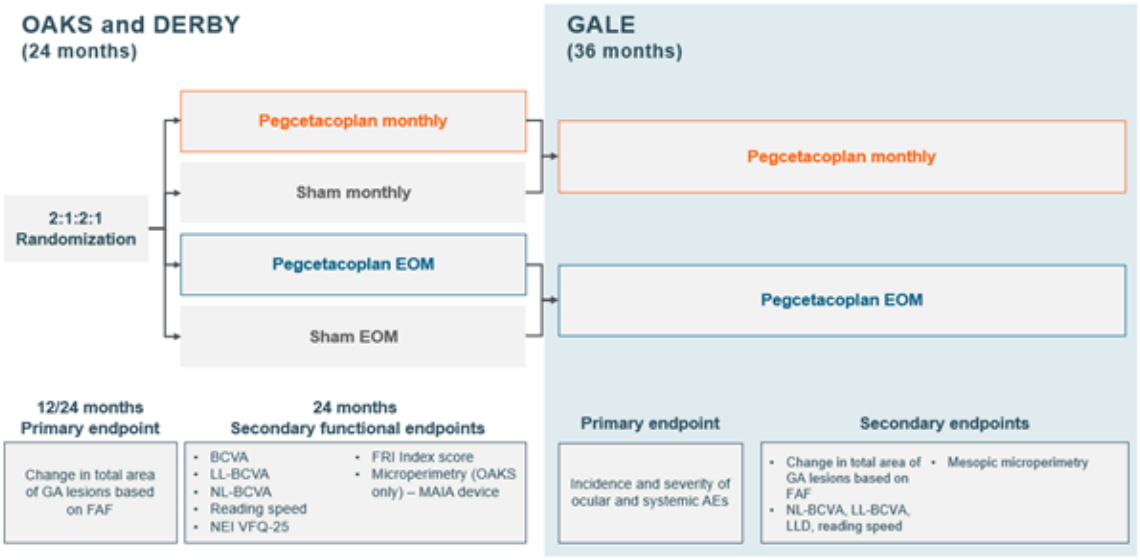
Dry AMD Symposium 2

Long-Term Efficacy of Pegcetacoplan in Patients With Geographic Atrophy

- Nathan Steinle, MD
- Chao Li
- Mark Burch
- Ramiro Ribeiro, PhD

Objective: To evaluate the long-term efficacy of pegcetacoplan in patients with geographic atrophy (GA) secondary to age-related macular degeneration.
Purpose: To report long-term efficacy data through 30 months of pegcetacoplan treatment from the GALE open-label extension study (at Month 6), and through 5 years based on data modelled from the 24-month OAKS and DERBY data.
Methods: In the OAKS (N=637; NCT03525600) and DERBY (N=621; NCT03525613) trials, patients were ≥60 years old with best-corrected visual acuity ≥24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and GA area between 2.5 mm^2 and 17.5 mm^2, or if multifocal, at least one focal lesion ≥1.25 mm^2 at baseline. Patients were randomized (2:2:1:1) to receive intravitreal pegcetacoplan monthly (PM) or every other month (PEOM), or sham monthly or every other month. The primary outcome measure was change from baseline in GA lesion area based on fundus autofluorescence. Patients had the opportunity to enter the GALE open-label extension study (NCT04770545) if they had completed the OAKS or DERBY trials through Month 24 (see **Figure**). This 30-month efficacy analysis was limited to patients who started on PM or PEOM regimens in OAKS and DERBY and continued the same regimen during GALE. For the 5-year modelling analysis, GA lesion growth rates between Months 12 and 24 in the PM and PEOM treatment arms from OAKS and DERBY were used to estimate the amount of time for pegcetacoplan-treated patients to reach the same GA lesion area as they would have without treatment. The modelling analysis assumes that the growth rate observed between Months 12 and 24 will continue linearly at the same rate beyond Month 24.
Results: In a prespecified pooled analysis of OAKS and DERBY at Month 24, pegcetacoplan reduced GA lesion growth versus sham by 21% ($p<0.0001$; nominal) and 17% ($p<0.0002$; nominal) for PM and PEOM, respectively. Long-term efficacy outcomes at Month 30 will be presented at the ASRS congress. From the 5-year modelling analysis, treatment with pegcetacoplan is estimated to delay the time to reach the 5-year untreated GA lesion area by 17.2 and 13.8 months in OAKS and 16.5 and 15.0 months in DERBY with PM and PEOM, respectively. When pooled, the estimated delay is 17.8 months and 14.0 months for PM and PEOM, respectively.
Conclusion: These long-term efficacy analyses demonstrate clinically meaningful reductions in GA lesion growth with pegcetacoplan through Month 30, with the potential to delay the progression of GA to central foveal involvement and preserve central vision.

IRB APPROVAL Yes



GALE open-label extension study design

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Effect of Pegcetacoplan on Photoreceptor and Retinal Pigment Epithelium Integrity in Geographic Atrophy in the Phase 3 Trials and GALE Extension Study

- Ursula Schmidt-Erfurth, MD
- Julia Mai
- Gregor Sebastian Reiter
- Wolf-Dieter Vogl
- Amir Sadeghipour
- Preeti Joshi
- Mark Burch
- Alex McKeown
- Hrvoje Bogunovic

Objective: Using OCT-based artificial intelligence analysis to quantify the loss of photoreceptor (PR) and retinal pigment epithelium (RPE) layer integrity in the disease activity and therapeutic response of pegcetacoplan (PEG) in geographic atrophy (GA) in OAKS, DERBY and the GALE extension study.
Purpose: To assess the effect of intravitreal PEG in the changes of PR and RPE layer integrity using deep learning analysis based on spectral domain optical coherence tomography (SD-OCT) over 30 months of follow-up and prospectively assess treatment effects at 6 months in patients crossing over from sham to treatment.
Methods: Patients with GA secondary to age-related macular degeneration in the OAKS and DERBY phase 3 trials were treated with intravitreal PEG, a complement C3 and C3b inhibitor, or sham. Patients were randomized 2:2:1:1 to receive PEG monthly (PM), every other month (PEOM), sham monthly, or sham EOM over 2 years. In the GALE open-label extension study, patients receiving PEG in OAKS and DERBY remained on the same regimen. Patients receiving sham in OAKS and DERBY transitioned to receiving PM or PEOM, at the same dosing frequency of sham injections they received in the phase 3 trials. OCT volumes from Spectralis SD-OCT were processed by deep learning-based image analyses using validated algorithms with convolutional neural networks identifying thinning and loss of the ellipsoid zone, defined as PR layer, and the RPE layer. Change from baseline in PR and RPE loss area was analyzed using mixed model for repeated measures methodology.
Results: At 24 months, change from baseline in PR and RPE loss area was significantly reduced by PEG in both trials, as evaluated by SD-OCT. In OAKS, PR loss was reduced in PM vs sham pooled by 52.7% ($p<0.0001$) and in PEOM vs sham pooled by 45.7% ($p<0.0001$), while RPE loss was reduced by 23.9% ($p<0.0001$) in PM vs sham pooled and by 21.4% ($p<0.0001$) in PEOM vs sham pooled. In DERBY, PR loss was reduced in PM vs sham pooled by 47.0% ($p<0.0001$) and in PEOM vs sham pooled by 45.8% ($p<0.0001$). RPE loss was reduced in PM vs sham pooled by 28.4% ($p<0.0001$) and in PEOM vs sham pooled by 21.2% ($p=0.0003$). Rates of PR and RPE loss over extended follow-up and particularly in patients transitioning from sham to PEG in the GALE extension study have been measured and will be presented for the first time.
Conclusion: OCT-based artificial Intelligence analysis can reliably identify and quantify loss of PR and RPE layers in disease activity and therapeutic maintenance in GA. Reductions in both PR and RPE degeneration were observed upon PEG therapy in the OAKS and DERBY phase 3 trials, providing further insight into the mechanism and outcomes for the potential first therapy in GA.

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Dry AMD Symposium 2

Retinal Tissue Preservation With Intravitreal Pegcetacoplan in Patients With Geographic Atrophy

- Sunir Garg, MD, FACS, FASRS
- Min Tsuboi
- Mark Burch
- Ramiro Ribeiro, PhD
- Daniel Jones
- Jeffrey Heier, MD

Objective: To assess the effect of pegcetacoplan on retinal tissue preservation in patients with Geographic Atrophy (GA) secondary to age-related macular degeneration from the OAKS and DERBY trials.
Purpose: Pegcetacoplan has demonstrated consistent efficacy vs sham in reducing GA lesion growth at 24 months. This analysis aims to contextualize this reduction in lesion growth with the amount of retinal tissue preserved with treatment.
Methods: The Phase 3 OAKS (N=637; NCT03525600) and DERBY (N=621; NCT03525613) trials enrolled patients ≥60 years old with best-corrected visual acuity ≥24 ETDRS letters and GA lesion area between 2.5 mm^2 and 17.5 mm^2, or if multifocal, at least one focal lesion ≥1.25 mm^2 at baseline. Patients were randomized (2:2:1:1) to receive intravitreal pegcetacoplan monthly (PM) or every other month (PEOM), or sham monthly or every other month. The primary endpoint was change from baseline in GA lesion area (mm^2) as measured by fundus autofluorescence. The amount of retinal tissue preserved (mm^2) at Month 24 with PM and PEOM treatment vs sham is reported for the overall study population and in the subgroup with nonsubfoveal (NSF) lesions (n=446) and informed by comparing absolute lesion growth from baseline among arms. Based on macular retinal pigment epithelium (RPE) density (cells/mm^2) reported in the literature, the number of RPE cells saved with pegcetacoplan was estimated.
Results: At Month 24, pegcetacoplan reduced GA lesion growth vs sham by 21% with PM and 17% with PEOM (both $p<0.0001$) based on the primary mixed-effects model for repeated measures analysis, and by 20% and 17% (both $p<0.0001$), respectively, from the piecewise linear slope analysis. These relative reductions in GA lesion growth equate to retinal tissue preservation of approximately 0.8 mm^2 (800,000 μm^2) with PM and 0.7 mm^2 (700,000 μm^2) with PEOM (**Figure 1**). In the NSF subgroup, the reductions in GA lesion growth vs sham of 26% for PM and 22% for PEOM (both $p<0.0001$) equate to 1.3 mm^2 (1,300,000 μm^2) and 1.1 mm^2 (1,100,000 μm^2), respectively, of retinal tissue saved with pegcetacoplan (**Figure 2**). All p-values are nominal. Based on macular RPE density reported in the literature, the estimated number of RPE cells saved with pegcetacoplan ranges from 3500 to 6300 in the overall study population and 5600 to 10,000 in the NSF subgroup.
Conclusion: Pegcetacoplan has consistently demonstrated clinically meaningful reductions in GA lesion growth vs sham. As this relative reduction translates to an absolute area of retinal tissue preserved, pegcetacoplan may save up to 10,000 RPE cells over 24 months.

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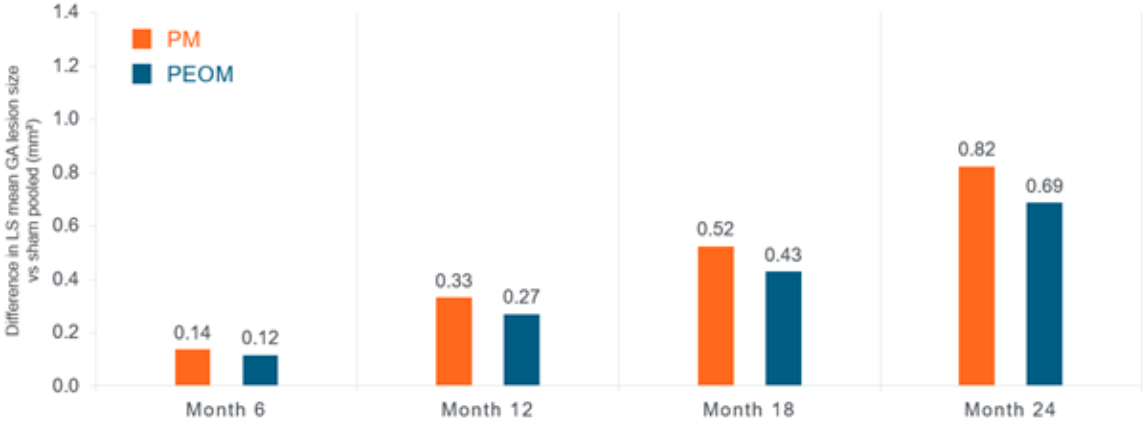
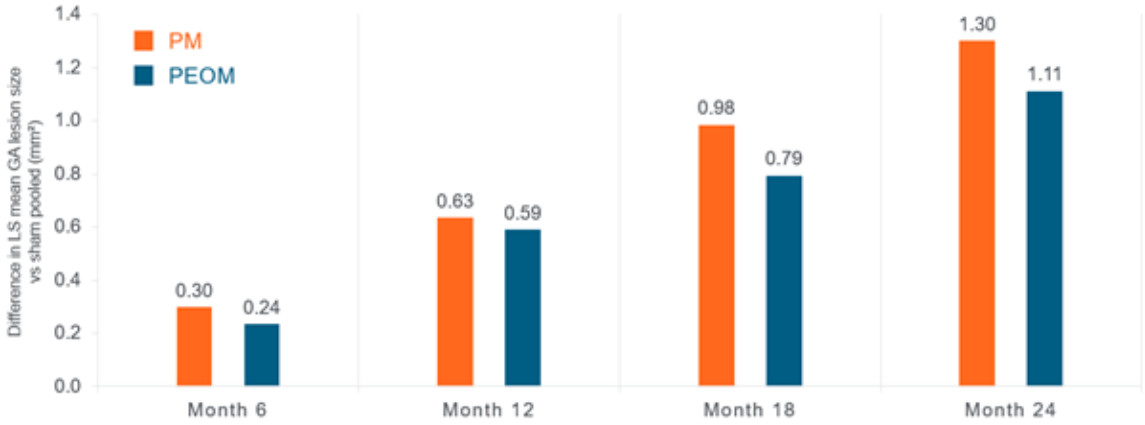


Absolute cumulative difference in lesion size vs pooled sham at Month 6, Month 12, Month 18, and Month 24 ('preserved area') from main MMRM analysis of mITT population. GA=geographic atrophy; LS=least squares; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; mITT=modified intent-to-treat.

Preservation of retinal tissue with pegcetacoplan in the overall population



Absolute cumulative difference in lesion size vs pooled sham at Month 6, Month 12, Month 18, and Month 24 ('preserved area') from main MMRM analysis of mITT population. GA=geographic atrophy; LS=least squares; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; mITT=modified intent-to-treat.

Preservation of retinal tissue with pegcetacoplan in nonsubfoveal lesions

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Dry AMD Symposium 2

Intravitreal Avacincaptad Pegol in Geographic Atrophy: Post-Hoc Analysis of Vision Loss From the GATHER Clinical Program

- Carl Danzig, MD
- Arshad Khanani, MD, MA, FASRS
- Sunil Patel, MD, PhD
- David Eichenbaum, MD, FASRS
- Jason Hsu, MD
- Charles Wykoff, MD, PhD, FASRS
- Jeffrey Heier, MD
- David Lally, MD
- Jared Nielsen, MD, MBA
- Veeral Sheth, MD, MBA, FASRS, FACS
- Peter Kaiser, MD FASRS

Objective: To evaluate the efficacy and safety of intravitreal avacincaptad pegol in geographic atrophy.
Purpose: Avacincaptad pegol (ACP), a pegylated RNA aptamer, binds to and specifically inhibits complement C5. Here we present results from two phase 3 pivotal trials evaluating efficacy and safety of intravitreal ACP in geographic atrophy (GA) patients.
Methods: GATHER1 and GATHER2 were multicenter, randomized, double-masked, sham-controlled trials. Both enrolled patients with non-centerpoint involving GA in part within 1500 µm from the foveal center. In GATHER1, 286 patients were randomized and treated with monthly ACP 1 mg, ACP 2 mg, or sham in Part 1 (1:1:1), or ACP 2 mg, ACP 4 mg , or sham in Part 2 (1:2:2). The prespecified primary endpoint was the mean rate of change in GA area over 12 months (square root transformed). In GATHER2, 447 patients were randomized and treated with monthly ACP 2 mg or sham (1:1) for the first 12 months. Similar to GATHER1, the prespecified primary endpoint was the mean rate of GA growth (slope analysis, square root transformed) from baseline to month 12. Safety was evaluated in both studies.

Results: In GATHER1, ACP 2 mg met the primary endpoint, demonstrating a significant reduction in mean rate of change in GA area (square root transformed) over 12 months (0.110 mm; p=0.0072) vs sham, with continuous treatment effect and separation from sham over 18 months. A consistent significant result was shown using observed (non-transformed) data, with a difference between ACP 2 mg and sham of 0.668 mm^2 (p=0.005) at 12 months. In GATHER2, ACP 2 mg also met the primary endpoint, demonstrating a significant reduction in the mean rate of GA growth (square root transformed) over 12 months (0.056 mm/yr; p=0.0064). GA growth rate was reduced regardless of analysis. Analyses using observed data showed that the mean rate of GA growth was 1.745 mm^2/yr with ACP 2 mg and 2.121 mm^2/yr with sham, demonstrating a reduction of 0.376 mm^2/yr (p=0.0039). The most common ocular treatment-emergent adverse events (TEAEs) in the study eye were related to the injection procedure in both treatment groups in both studies. In GATHER1, the incidence of ocular TEAEs over 12 months was 52.2% vs 34.5% with ACP 2 mg vs sham, respectively. In GATHER2, the incidence of ocular TEAEs over 12 months was 48.9% vs 37.4% with ACP 2 mg vs sham, respectively.
Conclusion: ACP is the first investigational GA therapy to achieve statistical significance for the 12-month primary endpoint vs sham, coupled with a consistent safety profile, in two phase 3 trials.

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Dry AMD Symposium 2

Ellipsoid Zone Integrity Preservation and Characterization of Ellipsoid Zone Integrity Features in the GATHER 1 Phase 2/3 Study

- Justis Ehlers, MD, FASRS
- Sari Yordi, MD
- Gagan Kalra, MD
- Hasan Cetin, MD
- Jon Whitney
- Conor McConville
- Yavuz Cakir, MD
- Victoria Whitmore
- Jamie Reese, RN
- Don Luo
- Sunil Srivastava, MD

Objective: Explore ellipsoid zone (EZ) integrity and EZ at-risk features in geographic atrophy (GA) and their association with therapeutic response and progression.
Purpose: EZ integrity can be a key marker of functional loss and progression risk in GA. This analysis evaluated multiple baseline EZ integrity and *EZ at-risk* features in advanced AMD in GATHER1.
Methods: GATHER1 was a randomized, double-masked phase 2/3 trial that evaluated avacincaptad pegol (ACP) in patients with GA. Baseline SD-OCT scans were imported into a machine learning-enhanced multi-layer retinal segmentation platform, enabling panmacular and zonal measures. Panmacular partial and total EZ attenuation (%) was determined by the percentage of macular cube with EZ-retinal pigment epithelium (RPE) thickness ≤20µm and EZ-RPE=0µm, respectively. Total EZ-GA gap (%) was calculated as the difference between EZ total attenuation and GA occupied areas, reflecting overall total EZ loss within areas of retina that have not developed GA (i.e., EZ loss excess). Partial EZ-GA gap (%) was calculated as the difference between EZ partial attenuation and GA area percentages. In addition, a novel deep learning model was used to evaluate *EZ at-risk* on each B-scan, and the *EZ at-risk* burden was calculated based on the percentage of macular volume occupied by *EZ at-risk*. These features were assessed at baseline and longitudinally assessed for therapeutic response and evaluated as risk factors for GA progression.
Results: At baseline, 260 eyes were included from GATHER1. Mean EZ partial attenuation was 45.78% [range:10.58–98.22%]; mean EZ total attenuation was 32.56% [range:3.89–82.66%]. Mean total EZ-GA gap was 11.08% [range:0–61.68%]. Mean partial EZ-GA gap was 24.31% [range:2.46–84.4%]. The mean *EZ at-risk* was 26.8% [range: 6.3–79.5%].

Longitudinal assessment of EZ attenuation at month 18 demonstrated ACP reduced partial EZ attenuation progression by 21% and reduced total attenuation progression by 22% compared to sham (Figure 1).

Conclusion: ACP demonstrated reduction in progressive EZ loss, a surrogate for photoreceptor loss. Multiple EZ integrity features were characterized and will be further evaluated for therapeutic biomarker potential as well as risk-stratification for disease progression.

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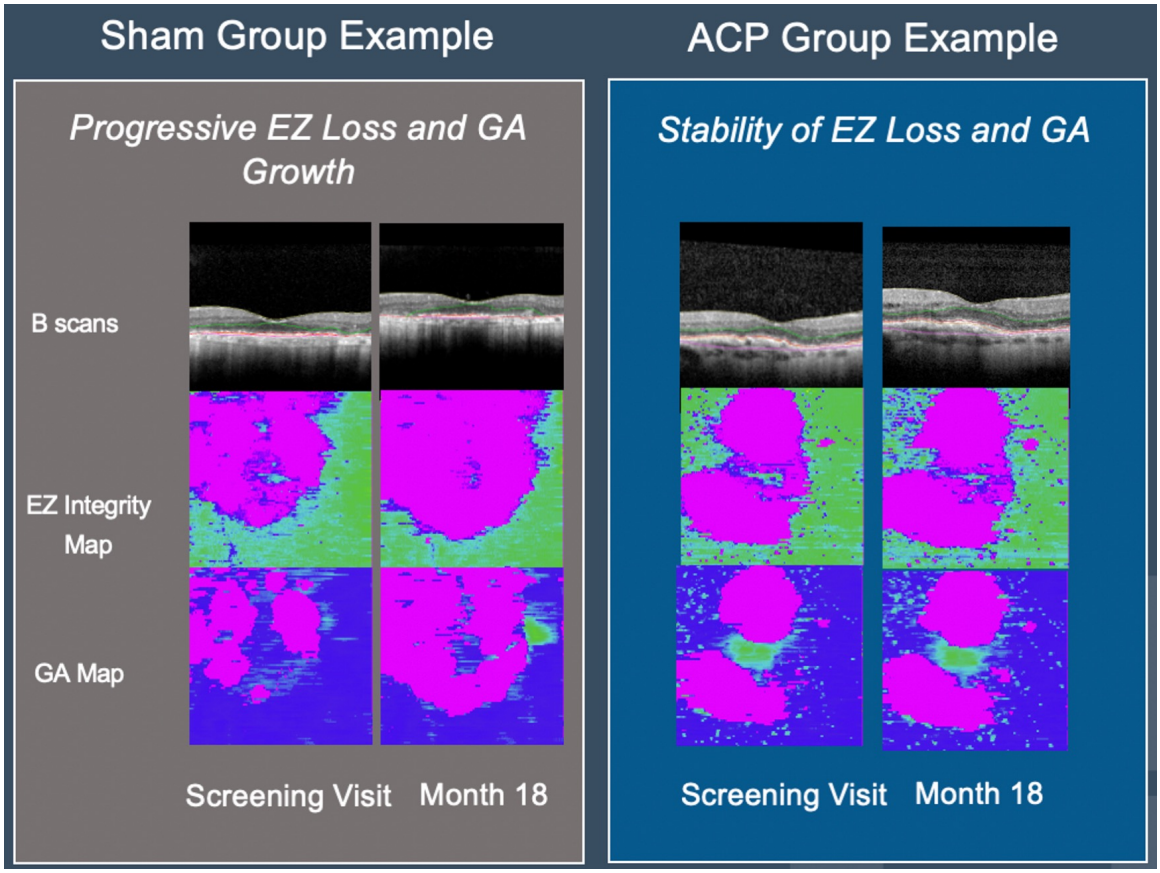
Sham Group Example
ACP Group Example
Progressive EZ Loss and GA Growth
Stability of EZ Loss and GA
B scans
EZ Integrity Map
GA Map
Screening Visit
Month 18
Screening Visit
Month 18

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Pegcetacoplan vs Avacincaptad Pegol in Patients With Geographic Atrophy: An Anchored Matching-Adjusted Indirect Comparison of the Phase 3 Trials

- Paul Hahn, MD, PhD, FASRS
- David Eichenbaum, MD, FASRS
- Sujata Sarda, PhD, MS
- Preeti Joshi
- Michele Intorcia, MSc
- Roger Luo, PhD, MS
- Priyanka Bobbili, ScD, MS
- Rose Chang, ScD, MS, MSPH
- Maryaline Catillon, PhD, MPH
- Chunyi Xu, MS
- Kirthana Sarathy, BS
- Mei Sheng Duh, ScD, MPH
- Varun Chaudhary, BSc, MD, FRSC(S)

Objective: To conduct a cross-trial comparison of GA lesion growth at Month 12 in patients with geographic atrophy (GA) treated with intravitreal pegcetacoplan (PEG) vs avacincaptad pegol (ACP) using an anchored matching-adjusted indirect comparison (MAIC).

Purpose: In the absence of a head-to-head trial, to compare reduction in GA lesion growth between PEG and ACP using MAIC anchored on a common sham injection control arm across trials.

Methods: This study used individual patient data (IPD) from the Phase 3 OAKS and DERBY trials of monthly 15 mg PEG vs sham and aggregate data from the Phase 3 GATHER2 trial of monthly 2 mg ACP vs sham. GATHER2 inclusion/exclusion (I/E) criteria were applied to IPD from OAKS and DERBY to select a similar subpopulation with nonsubfoveal GA, best corrected visual acuity (BCVA) worse than 20/25, and without fellow eye choroidal neovascularization. Propensity score weighting was used to balance key baseline variables selected a priori (e.g., age, GA laterality, lesion focality, BCVA, low-luminance BCVA, and GA lesion size). Change in GA lesion area from baseline to Month 12 was compared between OAKS and GATHER2 and between DERBY and GATHER2, separately, using MAIC, and the results were combined using meta-analysis. A secondary analysis compared efficacy in patients treated with every other month (EOM) 15 mg PEG vs monthly 2 mg ACP.

Results: The analysis included 103 patients from OAKS (61 PEG; 42 sham) and 102 patients from DERBY (49 PEG; 53 sham) meeting the I/E criteria from GATHER2, and 447 patients from GATHER2 (225 ACP; 222 sham). In OAKS vs GATHER2, the adjusted difference for change in GA lesion size between PEG and ACP after matching was –0.716 mm^2 (95% confidence interval: [CI]: –1.385, –0.046; $p<0.05$), a 37.0% statistically significant greater reduction in GA lesion growth for PEG vs ACP. In DERBY vs GATHER2, the adjusted difference for change in GA lesion size between PEG and ACP after matching was –0.234 mm^2 (95% CI: –1.354, 0.885; $p=0.68$), a 12.1% numerically greater reduction in GA lesion growth for PEG vs ACP. The pooled effect for PEG vs ACP was –0.589 mm^2 (95% CI: –1.164, –0.014; $p<0.05$), a 30.4% statistically significant greater reduction in change in GA lesion growth with PEG vs ACP. Analysis of less frequent dosing of EOM PEG vs monthly ACP demonstrated comparable efficacy between the two groups.
Conclusion: In the absence of a head-to-head trial, this MAIC in patients with GA suggests a greater reduction in observed GA lesion growth with monthly PEG vs ACP at Month 12.

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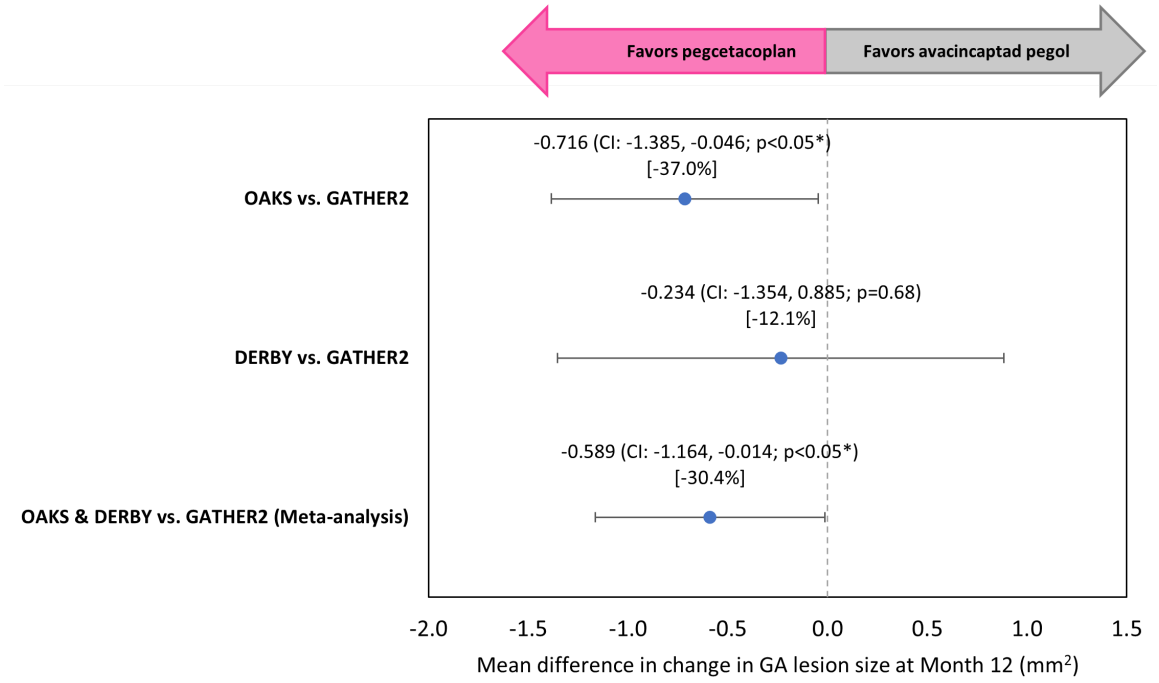

Monthly PEG vs ACP in OAKS, DERBY and GATHER2: MAICs and meta-analysis