AMERICAN ACADEMY OF OPHTHALMOLOGY®

Avacincaptad Pegol for Geographic Atrophy Secondary to Age-Related Macular Degeneration

Two-Year Efficacy and Safety Results from the GATHER2 Phase 3 Trial

Arshad M. Khanani, MD, MA,[1,2] Carl J. Danzig, MD,[3] Jeffrey S. Heier, MD,[4] Glenn J. Jaffe, MD,[5] Peter K. Kaiser, MD,[6] David R. Lally, MD,[7] Sunil S. Patel, MD, PhD,[8] Lejla Vajzovic, MD,[5] Christina Y. Weng, MD, MBA,[9] Hersh Patel, OD,[10] Julie Clark, MD, MS,[10] Dhaval Desai, PharmD,[10] Don Luo, PhD,[10] Erin Henry, PhD,[10] Frank G. Holz, MD,[11] on behalf on the GATHER2 Trial Investigators

Purpose: Avacincaptad pegol (ACP) is a pegylated RNA aptamer that inhibits complement C5. The efficacy and safety of ACP 2 mg was investigated in GATHER2, with positive year 1 results published. Herein, 2-year results are reported.

Design: Phase 3, randomized, sham-controlled study (ClinicalTrials.gov identifier, NCT04435366).

Participants: Patients with non–center point-involving geographic atrophy (GA).

Methods: Eligible patients were randomized 1:1 to receive monthly ACP 2 mg (n = 225) or sham (n = 222) for 1 year. At month 12, patients who received ACP 2 mg were randomized again 1:1 to dosing every month (EM; n = 96) or every other month (EOM; n = 93) with ACP 2 mg. Patients who had received monthly sham continued with sham (n = 203).

Main Outcome Measures: The safety and efficacy of ACP versus sham administration over 2 years and the effect of ACP EM or EOM dosing in year 2.

Results: Overall, 175 and 184 patients in the ACP and sham group completed the study at year 2, respectively. At 2 years, treatment with ACP demonstrated a continued reduction in GA growth (slope) with both ACP EM and EOM versus sham. From baseline to year 2, the mean rate of GA area growth was 4.46 mm^2 (standard error [SE], 0.25 mm^2) with ACP EM and 5.18 mm^2 (SE, 0.17 mm^2) with sham, a difference in growth of 0.724 mm^2 (95% confidence interval [CI], 0.133–1.315 mm^2; $P = 0.0165$), representing a 14% difference. From baseline to year 2, the mean rate of GA area growth was 4.20 mm^2 (SE, 0.25 mm^2) with ACP EOM, a difference in growth of 0.976 mm^2 (95% CI, 0.377–1.575 mm^2; nominal $P = 0.0015$) versus sham, representing a 19% difference. The incidence of choroidal neovascularization (study eye) was 11.6% with ACP (all treated) versus 9.0% with sham over 2 years. No events of retinal vasculitis, ischemic optic neuropathy, or serious intraocular inflammation occurred over 2 years.

Conclusions: Dosing of ACP 2 mg, either EM or EOM, continued to reduce GA growth versus sham therapy over 2 years with no new safety signals compared with year 1.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology 2026;133:451-465 © 2025 by the American Academy of Ophthalmology. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Supplemental material available at www.aaojournal.org.

Geographic atrophy (GA) is a form of late-stage age-related macular degeneration (AMD) characterized by clearly demarcated atrophic lesions of the macula.[1,2] Geographic atrophy is known to result in the progressive loss of retinal tissue, which may lead to permanent central vision loss, and as a result, may affect quality of life, functioning, and independence negatively in those affected.[2–5] It is widely accepted that the pathophysiologic characteristics of GA are multifactorial and remain to be elucidated fully. However, dysregulation of the complement pathway has been implicated based on several lines of scientific evidence.[1,6–11] In 2023, 2 therapies were approved by the United States Food and Drug Administration (FDA), both of which are inhibitors of the complement pathway and whose arrival marked the availability of the first treatments for GA.[12–14] One of these therapies is avacincaptad pegol (ACP; Izervay [Astellas Pharma Inc]), which was approved in the United States by the FDA in

© 2025 by the American Academy of Ophthalmology
Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
https://doi.org/10.1016/j.ophtha.2025.12.011
ISSN 0161-6420/25

August 2023 as a monthly intravitreal injection for up to 1 year at a dose of 2 mg for the treatment of GA secondary to AMD.[13,15] Avacincaptad pegol is a novel RNA aptamer with a unique branched polyethylene glycol that specifically inhibits cleavage of complement C5 and is thought to slow GA progression by preventing the production of terminal, active C5 cleavage products (C5a and C5b), thereby inhibiting downstream inflammation and retinal cell death.[15,16] Targeting C5 has a potential advantage over upstream targets because it preserves host defense functions while inhibiting inflammasome activation and membrane attack complex formation.[17] The efficacy and safety of ACP 2 mg was investigated in the GATHER1 and GATHER2 trials, and it was the first therapy for GA to meet the prespecified primary objective at 1 year in 2 sham-controlled pivotal studies in patients with non−center point-involving GA.[15,16] In the phase 2/3 GATHER1 trial (ClinicalTrials.gov identifier, NCT02686658), with monthly ACP 2 mg, statistically significant reductions in the mean rate of GA growth (square root transformed) were noted compared with sham administration over 1 year (difference, 0.110 mm; 95% confidence interval [CI], 0.030−0.190 mm; P = 0.007), which were maintained throughout the 18-month study. Treatment was well tolerated over 18 months after monthly intravitreal administration of ACP 2 mg.[16,18] In the phase 3 GATHER2 trial, with monthly ACP 2 mg treatment, statistically significant reductions of 0.056 mm/year (95% CI, 0.016−0.096 mm/year; P = 0.006) were noted in GA growth (slope) using square root-transformed data and 0.376 mm^2/year (95% CI, 0.122−0.631 mm^2/year; P = 0.004) using observed data compared with sham administration over year 1. Monthly ACP 2 mg was well tolerated through year 1 with no cases of endophthalmitis, intraocular inflammation, ischemic optic neuropathy, or retinal vasculitis.[15] Herein, efficacy and safety results over 2 years of the GATHER2 trial are reported, assessing alternate dosing regimens of every month (EM) and every other month (EOM) dosing of ACP 2 mg during year 2 compared with sham therapy in patients with GA.

Methods

Study Design

The GATHER2 study was a 2-year, phase 3, multicenter, randomized, double-masked, sham-controlled clinical trial (ClinicalTrials.gov identifier, NCT04435366). Full methodology relevant to year 1 was published previously.[15] In brief, GATHER2 enrolled patients from 205 sites in 20 countries and was conducted in full compliance with the principles of the Declaration of Helsinki and in compliance with the respective law and regulations of the country in which the study was conducted. In addition, the study was performed in line with the principles outlined in the Guideline for Good Clinical Practice (International Council for Harmonisation [ICH], version E6), the International Council for Harmonization of Technical Requirements for Better Health Tripartite Guideline (May 1997), and FDA regulations. The clinical study protocol, any amendments, and the patient-informed consent provisions were reviewed and approved by the appropriate independent ethics committee or institutional review board for each center involved in the study (a list of IRBs is available at www.aaojournal.org), according to national or local regulations and in accordance with the FDA Title 21 Code of Federal Regulations parts 56.107 through 56.115 and the International Council for Harmonization Good Clinical Practice guidelines (Committee for Proprietary Medicinal Products/ICH/135/95). The following changes were made from protocol-planned analyses: (1) time to visual acuity (VA) loss analysis based on best-corrected visual acuity (BCVA) was added after primary analysis of year 1, (2) GA growth rate without square root transformation, and (3) piecewise analysis by every 6-month interval on GA growth rate.

Patients

Full details on inclusion and exclusion criteria were published previously.[15] In short, eligible patients had to be 50 years of age or older; had to have non−center point-involving GA in the study eye; had to have a BCVA of 20/25 to 20/320 in the study eye; had to have a GA lesion in part within 1500 μm from the foveal center, with a total area of 2.5 to 17.5 mm^2 (1−7 disc areas), as determined by screening fundus autofluorescence (FAF) images in the study eye (if multifocal lesions were present, at least 1 lesion had to be at least 1.25 mm^2 [0.5 disc areas]); had to have no macular atrophy secondary to any condition other than AMD in either eye; had to have undergone no previous treatment for AMD or any previous intravitreal treatment for any indication in either eye, with the exception of oral vitamin or mineral supplements; and had to have no choroidal neovascularization (CNV) in either eye.

Randomization and Masking

On day 1, study eyes were randomized 1:1 to either ACP 2 mg EM (100 μl of a 20-mg/ml solution for injection) or sham therapy using an interactive response technology system that stratified by factors known to be of prognostic importance in AMD. After the collection of data for the primary end point analyses at year 1, eyes that received ACP 2 mg EM and remained in the study at month 12 were randomized again 1:1 using the same procedure as for the initial randomization to continue receiving either ACP 2 mg EM or ACP 2 mg EOM, alternating with sham administration from months 12 to 23. Eyes that initially were randomized to sham administration at day 1 continued to receive monthly sham procedures through month 23 (Fig S1, available at www.aaojournal.org). All patients underwent a final follow-up visit at month 24. To preserve the integrity of the study data through the final database lock at year 2, masking was maintained except for selected sponsor team members who were unmasked for the year 1 assessment. All unmasked personnel remained unmasked and were not involved in the study management for year 2. All patients and masked site staff remained masked. Please see the Supplemental Appendix (available at www.aaojournal.org) for further details.

Outcomes

Over 2 years, the prespecified primary efficacy objective was GA lesion size measured by FAF at 5 time points (baseline, month 6, month 12, month 18, and month 24), which was analyzed using a slope analysis of observed or non−square root-transformed data to determine the mean rate of GA growth from baseline to year 2 for ACP 2 mg EM and EOM compared with sham administration. This analysis differs from the prespecified primary objective for year 1 of GA lesion size measured by FAF in at least 3 time points (baseline, month 6, and month 12), which was analyzed using a slope analysis of square root-transformed data to determine the

mean rate of GA growth from baseline to year 1 for ACP 2 mg EM compared with sham administration. The rate of persistent VA loss, defined as loss of 15 or more ETDRS letters from baseline at 2 or more consecutive visits up to year 2, and change in BCVA and low-luminance (LL) BCVA from baseline to year 2 were prespecified end points for the year 2 analysis. A prespecified piecewise analysis at 6-month intervals was performed to determine treatment effect over 2 years. A prespecified exploratory subgroup analysis based on baseline patient and lesion characteristics was performed to evaluate consistency of treatment response over 2 years. Safety assessments in year 2 were consistent with the safety assessments in year 1 and included adverse events (AEs), serious AEs, vital signs, ophthalmic findings, 12-lead electrocardiography findings, and laboratory variables. Suspected development of CNV in the study eye was followed by a full imaging workup assessed with fundus photography, fluorescein angiography, and OCT and confirmed by the Duke Reading Center. In eyes with GA and new-onset CNV and in eyes with GA and no CNV, GA area was measured on FAF images with RegionFinder software (Heidelberg Engineering) with assistance from OCT and near-infrared reflectance images to help define the GA boundaries (Table S1, available at www.aaojournal.org). Details about the grading methodology used in this study were published previously.[19] For study eyes that demonstrated CNV, treatment with ranibizumab or aflibercept was provided according to their label, and the patients continued in the trial. Please see the Supplemental Appendix for further details.

Statistical Analyses

Statistical analyses were conducted using SAS version 9.4 software (SAS Institute) or R software (R Foundation for Statistical Computing). Three analysis sets were defined for year 2: intention-to-treat (ITT) analysis set (all randomized patients who received at least 1 dose of study drug), safety analysis set (all patients who received at least 1 dose of study drug), and re-randomized analysis set (the subset of the ITT analysis set who were randomized again at month 12 or who were receiving sham administration and completed the month 12 visit). For the ITT and safety analysis sets, ACP 2 mg and sham administration were used as treatment groups, and patients who were discontinued from the study in year 1 were included. For the re-randomized analysis set, ACP 2 mg EM, ACP 2 mg EOM, and sham administration were used as treatment groups, and patients who were discontinued from the study in year 1 were excluded. To control for multiplicity and overall type 1 error at a 5% 2-sided significance level, year 2 statistical significance was conducted sequentially on prespecified outcomes in the following order: (1) hypothesis testing in ACP 2 mg EM vs sham groups for mean GA growth rate (slope) from baseline over 2 years, (2) hypothesis testing in ACP 2 mg (EM and EOM combined) versus sham groups for time to persistent VA loss of 15 or more letters in at least 2 consecutive visits from baseline over 2 years using the Kaplan-Meier method with a log-rank test, and (3) hypothesis testing in ACP 2 mg EOM versus sham groups for mean GA growth rate (slope) from baseline over 2 years.

For the analysis of GA growth rate, a mixed model for repeated measures (MMRM) was applied to all available data using a response variable of the GA area over time from baseline up to month 24 in 5 time points: baseline, month 6, month 12, month 18, and month 24. The MMRM was used to assess the difference between the treatment groups in terms of the rate of growth (slope, measured in square millimeters per year) of the GA area over time through 24 months. Time was defined as a continuous variable in number of study days since the baseline assessment. Treatment groups included ACP 2 mg EM, ACP 2 mg EOM, and sham therapy of the re-randomized analysis set. In the primary analysis at year 1, the square root transformation of GA area was used, although the mean GA growth (slope) notably has shown similar results with or without square root transformation. Therefore, in the year 2 analysis, the untransformed GA growth using observed GA area of measurement was used as the end point, and this decision was made before the year 1 data were unmasked. An unstructured covariance structure was used in the MMRM for the within-patient correlations. Missing at random was assumed in the MMRM by the restricted maximum likelihood method for the mean growth GA analysis, where the observed data were used with no imputation. The piecewise analysis by every-6-month intervals with knots at months 6, 12, and 18 was assessed by an MMRM that assumed a linear growth rate of GA, which was used to provide more detail on the GA growth curve by interval over 2 years. The MMRM described above was used to fit every-6-month interval data.

Time to persistent VA loss was defined as the time to the first occurrence of a loss of 15 or more ETDRS letters in 2 or more consecutive visits from baseline up to year 2 for the ITT analysis set. Patients without a persistent VA loss event were censored at the last assessment of BCVA before the end of the study or at randomization if no BCVA assessment after baseline was available. The time-to-event analysis was conducted using the Kaplan-Meier method with a log-rank test and a Cox proportional hazards regression model with the hazard ratio (HR) and associated 2-sided 95% CI. Statistical significance of testing with the P value from the log-rank test was used in the hierarchical testing procedure. Recognizing that time to persistent VA loss analysis depends on the thresholds of the loss of ETDRS letters, the following sensitivity analyses on different thresholds were performed: BCVA loss of 10 or more or 20 or more ETDRS letters from baseline in 2 or more consecutive visits up to year 2. The mean change in BCVA from baseline to year 2 in the ACP 2-mg treatment group was compared with sham administration using an MMRM with change from baseline as the response; visit, treatment, and treatment-by-visit interaction as fixed effects; and patient as random effect on the ITT analysis set. The mean change in LL BCVA from baseline to year 2 was analyzed similarly as in the BCVA analysis described above with change from baseline of LL BCVA as the response variable. An MMRM analysis was performed for the prespecified exploratory subgroup analysis based on baseline patient and lesion characteristics. The following subgroups were included based on the presence of at least 25 patients for each group: baseline VA of 50 or more ETDRS letters, size of baseline GA ($<$ 4 disc areas vs. $\geq$ 4 disc areas), pattern of FAF at the junctional zone of GA (banded or diffuse), age ($<$ 75 years vs. $\geq$ 75 years), and sex (male vs. female). Difference in growth rate between groups was calculated as sham minus ACP.

All safety analyses were performed on the safety analysis set and re-randomized analysis set, and they included analysis of data generated from the first dose of study drug until 30 days after the last dose or the last follow-up visit, whichever came later. Safety analyses focused on the year 2 (months 13−24) data also were performed. The analyses were conducted according to the treatment received, which includes any patient who received an injection of ACP 2 mg even if they did not complete the 24 months of the clinical trial. Hence, all patients administered ACP 2 mg at any time point were analyzed in the ACP 2 mg group. Missing values of safety data were not imputed, and safety summaries were based on the observed patients. Patients with errors in treatment allocation who were randomized (regardless of error) but were not

treated were excluded for all efficacy and safety analyses. These patients were included in the summary of patient dispositions. If patients were treated but not randomized, then by definition they were excluded from the efficacy analyses because randomization is missing but were reported under the treatment they actually received for all safety analyses. Patients who were randomized but were administered the incorrect treatment at any time during the study were reported under the randomized treatment group for efficacy analyses as part of the ITT population but were reported under the treatment they actually received for all safety analyses as part of the safety population. Specifically, this implies that for safety analyses, any patient who ever received ACP was included in the ACP group based on actual injections received. For the re-randomized population who were administered the incorrect treatment after re-randomized, patients were reported under the re-randomized treatment group for efficacy and safety analyses. Please see the Supplemental Appendix for further details.

Results

Patient Disposition and Baseline Demographics and Characteristics

Overall, 1422 patients were screened between June 22, 2020, and July 23, 2021, with 448 eyes of 448 patients randomized at baseline (225 eyes to monthly ACP 2 mg and 223 eyes to monthly sham administration), which included 1 eye randomized to the sham group that was not treated. Of the 189 patients assigned to the ACP 2 mg group who were randomized again after the primary analysis at year 1, 96 patients were assigned to ACP 2 mg EM, and 93 patients were assigned to ACP 2 mg EOM in year 2. Of the 223 patients initially assigned to re-randomized the sham group, 203 patients remained in the study at the end of year 1 and continued in the sham group in year 2. The proportion of patients in the re-randomized analysis set who completed the study through year 2 was similar in the ACP 2 mg EM, ACP 2 mg EOM, and sham administration groups (92.7%, 89.2%, and 90.6%, respectively). The reasons for early study discontinuation were similar across all 3 treatment groups and were reported with a comparably low frequency (request by patient, AE, death, lost to follow-up, and patient noncompliance all $< 5\%$; Fig 1). Further details on the patients in the re-randomized analysis set who withdrew from the study after year 1 are in Table S2 (available at www.aaojournal.org).

Baseline demographics and characteristics from the ITT analysis set were published previously.[15] In the re-randomized analysis set, which had the same stratification factors applied as the ITT analysis set, baseline demographics and characteristics were well balanced among the 3 treatment groups. Most patients were White and female, and the mean age was 76.2 years for the ACP 2 mg EM group, 77.8 years for the ACP 2 mg EOM group, and 77.5 years for the sham group (Table 1).

Efficacy Analyses

The prespecified year 2 primary objective of a reduction in mean rate of GA growth (slope) with ACP 2 mg EM dosing versus sham administration was met. From baseline to year 2, the annualized mean rate of GA area growth (slope) was 2.23 mm^2/year (standard error [SE], 0.124 mm^2/year) with ACP 2 mg EM versus 2.59 mm^2/year (SE, 0.085 mm^2/year) with sham administration, an absolute difference of 0.362 mm^2/year (95% CI, 0.066−0.657 mm^2/year; $P = 0.0165$). Over 2 years, the mean rate of GA area growth (slope) was 4.46 mm^2 (SE, 0.25 mm^2) with ACP 2 mg EM versus 5.18 mm^2 (SE, 0.17 mm^2) with sham administration, an absolute difference of 0.724 mm^2 (95% CI, 0.133−1.315 mm^2), representing a 14% difference in GA area growth between ACP 2 mg EM and sham administration. Because of the hierarchical testing procedure, no statistical test was performed for the ACP 2 mg EOM treatment group. From baseline to year 2, the annualized mean rate of GA area growth (slope) was 2.10 mm^2/year (SE, 0.126 mm^2/year) with ACP 2 mg EOM vs sham administration, with an absolute difference of 0.488 mm^2/year (95% CI, 0.189−0.788 mm^2/year; nominal $P = 0.0015$). Over 2 years, the mean rate of GA area growth (slope) was 4.20 mm^2 (SE, 0.25 mm^2) with ACP 2 mg EOM versus sham administration, an absolute difference of 0.976 mm^2 (95% CI, 0.377−1.575 mm^2), representing a 19% difference in GA area growth between ACP 2 mg EOM and sham administration (Fig 2A). A post hoc analysis was performed to assess the mean rate of GA area growth (slope) using square root-transformed data (Fig 2B). From baseline to year 2, the mean rate of GA area growth (slope) was 0.368 mm (SE, 0.029 mm) with ACP 2 mg EM and 0.411 mm (SE, 0.028 mm) with sham administration, with an absolute difference of 0.043 mm (95% CI, 0.003−0.084 mm; nominal $P = 0.0362$), representing an 11% difference in GA area growth between ACP 2 mg EM and sham administration. From baseline to year 2, the mean rate of GA area growth (slope) was 0.339 mm (SE, 0.03 mm) with ACP 2 mg EOM versus sham administration, with an absolute difference of 0.072 mm (95% CI, 0.031−0.113 mm; nominal $P = 0.0006$), representing an 18% difference in GA area growth between ACP 2 mg EOM and sham administration. These results were consistent with the slope analysis using observed data (Fig 2A). Of note, all eyes received monthly ACP 2 mg or monthly sham administration in year 1, and a post hoc analysis of the mean change in GA area using observed data from baseline per visit was performed to visualize the difference better (Fig S2, available at www.aaojournal.org). Results were consistent with the slope analysis using observed data (Fig 2A). The piecewise analysis by every-6-month intervals showed that ACP 2 mg EM and ACP 2 mg EOM reduced the mean rate of GA growth compared with sham administration as early as month 6 (Fig 3A). The treatment effect of ACP 2 mg EM and ACP 2 mg EOM continued to increase over time compared with sham administration over 2 years and more than doubled compared with year 1 (Fig 3B). The difference in the mean rate of GA growth between ACP 2 mg EM and sham administration was 0.31 mm^2 from baseline to year 1 and 0.81 mm^2 from baseline to year 2, respectively. The difference in the mean rate of GA growth between ACP 2 mg EOM and sham

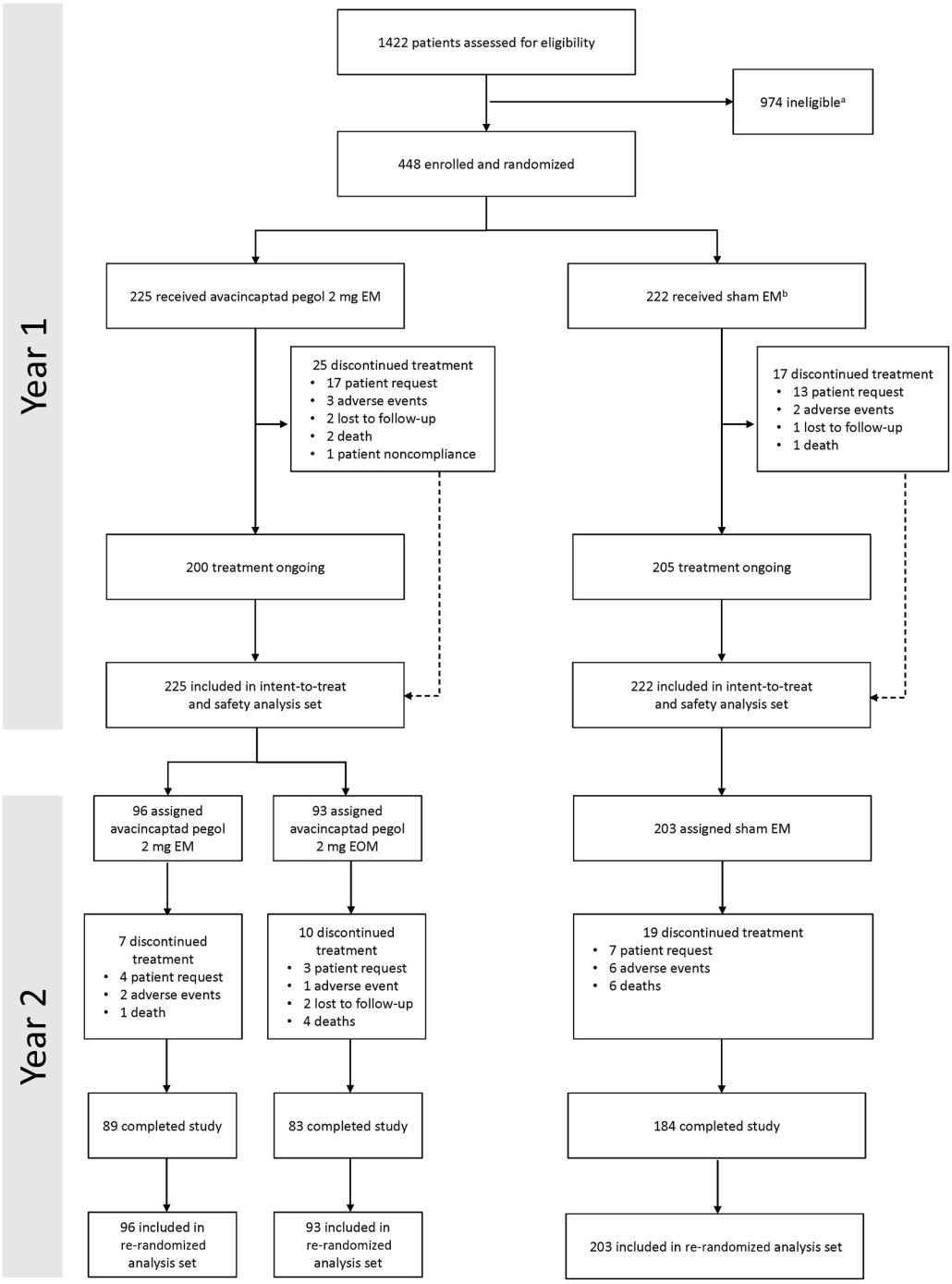

Figure 1. Flow diagram showing patient disposition. [a]Most common (> 95%) reason for ineligibility was related to not meeting specific ophthalmologic inclusion criteria or meeting exclusion criteria. [b]Two hundred twenty-three patients were randomized to sham administration, but 1 patient did not receive treatment because of withdrawal of consent before the baseline visit and was not included. There were 175 patients treated with ACP 2 mg out of 225 from the initial randomization to the end of the study (ITT population). There were 172 patients treated with ACP 2 mg out of 189 who were re-randomized to ACP 2 mg EM and EOM in Year 2 who completed the study (re-randomized population). EM = every month; EOM = every other month.

administration was 0.41 mm^2 from baseline to year 1 and 1.04 mm^2 from baseline to year 2, respectively.

Change in BCVA and LL BCVA from baseline to year 2 was a prespecified analysis. In the ITT analysis set, the least-squares mean change in BCVA from baseline to year 2 was −7.31 ETDRS letters for ACP 2 mg and −6.48 ETDRS letters for sham administration. The least-squares mean change in LL BCVA from baseline to year 2 was −10.58 ETDRS letters for ACP 2 mg and −9.1 ETDRS letters for sham administration (Table 2). These results were

Table 1. Baseline Demographics and Characteristics (Re-Randomized Analysis Set)

Characteristic	Avacincaptad Pegol 2 mg Every Month to Every Month (n = 96)	Avacincaptad Pegol 2 mg Every Month to Every Other Month (n = 93)	Sham Administration (n = 203)
Age (yrs)	76.2 (9.41)	77.8 (8.12)	77.5 (8.7)
Sex			
Female	70 (72.9%)	58 (62.4%)	144 (70.9%)
Male	26 (27.1%)	35 (37.6%)	59 (29.1%)
Race or ethnicity			
White	85 (88.5%)	73 (78.5%)	169 (83.3%)
Asian	0	0	1 (0.5%)
Black or African American	0	0	1 (0.5%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Pacific Islander	0	0	0
Other	3 (3.1%)	5 (5.4%)	12 (5.9%)
Not reported	8 (8.3%)	15 (16.1%)	20 (9.9%)
Hispanic or Latino	11 (11.5%)	11 (11.8%)	21 (10.3%)
Current smoking status			
Active	46 (47.9%)	41 (44.1%)	97 (47.8%)
Nonactive	50 (52.1%)	52 (55.9%)	106 (52.2%)
Total GA area (mm^2)*	7.24 (4.18)	7.34 (3.74)	7.78 (3.88)
GA lesion focality*			
Unifocal	20 (20.8%)	18 (19.4%)	42 (20.7%)
Multifocal	76 (79.2%)	75 (80.6%)	161 (79.3%)
Hyperautofluorescence pattern*			
Diffuse or banded	92 (95.8%)	90 (96.8%)	199 (98.0%)
Focal or none	4 (4.2%)	3 (3.2%)	4 (2.0%)
Lens status*			
Phakic	44 (45.8%)	47 (50.5%)	88 (43.3%)
Pseudophakic	52 (54.2%)	46 (49.5%)	115 (56.7%)
Mean BCVA (letters)*	71.4 (9.19%)	71.0 (8.91%)	71.8 (9.24%)
Mean LL BCVA (letters)*	41.5 (19.4)	42.5 (18.88)	40.6 (19.65)

BCVA = best-corrected visual acuity; GA = geographic atrophy; LL = low-luminance.
Data are presented as no. (%) or mean (SD). Baseline was the last available measurement before the first administration of study drug. The mean value of the screening and day 1 visual acuity score was used as the baseline value for BCVA. The screening visual acuity score was used as the baseline value for LL BCVA. The avacincaptad pegol 2 mg every-other-month group received monthly avacincaptad pegol 2 mg in the first year (avacincaptad pegol 2 mg every month to every other month).
*Study eye.

consistent with a post hoc analysis of different tiers of BCVA, with no difference between ACP 2 mg and sham administration at year 2 (Table S3, available at www.aaojournal.org). Prespecified time-to-event analyses were conducted on the ITT analysis set to characterize the patient journey of VA loss by accounting for the incidence of clinically significant and persistent VA loss from baseline to year 2, supporting disease stabilization. The risk probability of persistent VA loss of 15 or more ETDRS letters from baseline up to year 2 was 18% for ACP 2 mg compared with 19% for sham administration (HR, 0.90; 95% CI, 0.57−1.42; $P = 0.6424$, log-rank test; Fig 4). The VA trends over time with BCVA loss of 10 or more and 20 or more letters from baseline to year 2 measured at any 2 or more consecutive visits were consistent with the findings in BCVA loss of 15 or more letters (Fig S3, available at www.aaojournal.org). The risk probability for experiencing persistent VA loss of 10 or more letters was 31% with ACP 2 mg and 34% with sham administration (HR, 0.88; 95% CI, 0.62−1.24; $P = 0.4591$, log-rank test). The risk probability for experiencing persistent VA loss of 20 or more letters was 10% with ACP 2 mg and 14% with sham administration (HR, 0.69; 95% CI, 0.38−1.23; $P = 0.2025$, log-rank test).

Overall, the exploratory subgroup analyses by baseline demographics and clinical characteristics were consistent with the overall population. The mean rate of growth (slope) in GA area from baseline to year 2 for ACP 2 mg EM and ACP 2 mg EOM was consistently lower than that of the sham administration across all prespecified subgroup analyses (Fig S4, available at www.aaojournal.org).

Safety Analysis

Safety evaluations reported here are from the safety analysis set (all ITT patients over 2 years), with select tables referring to safety between year 1 and year 2. In the safety analysis set, ocular treatment-emergent AEs (TEAEs) in the study eye occurred in 144 patients (64.0%) with ACP 2 mg and 107 patients (48.2%) with sham administration over 2 years (Table 3). Over 2 years, the most commonly reported ($\geq$ 2% of study eyes in any treatment group) ocular TEAEs were conjunctival hemorrhage, CNV, punctate keratitis, elevated intraocular pressure (IOP), conjunctival

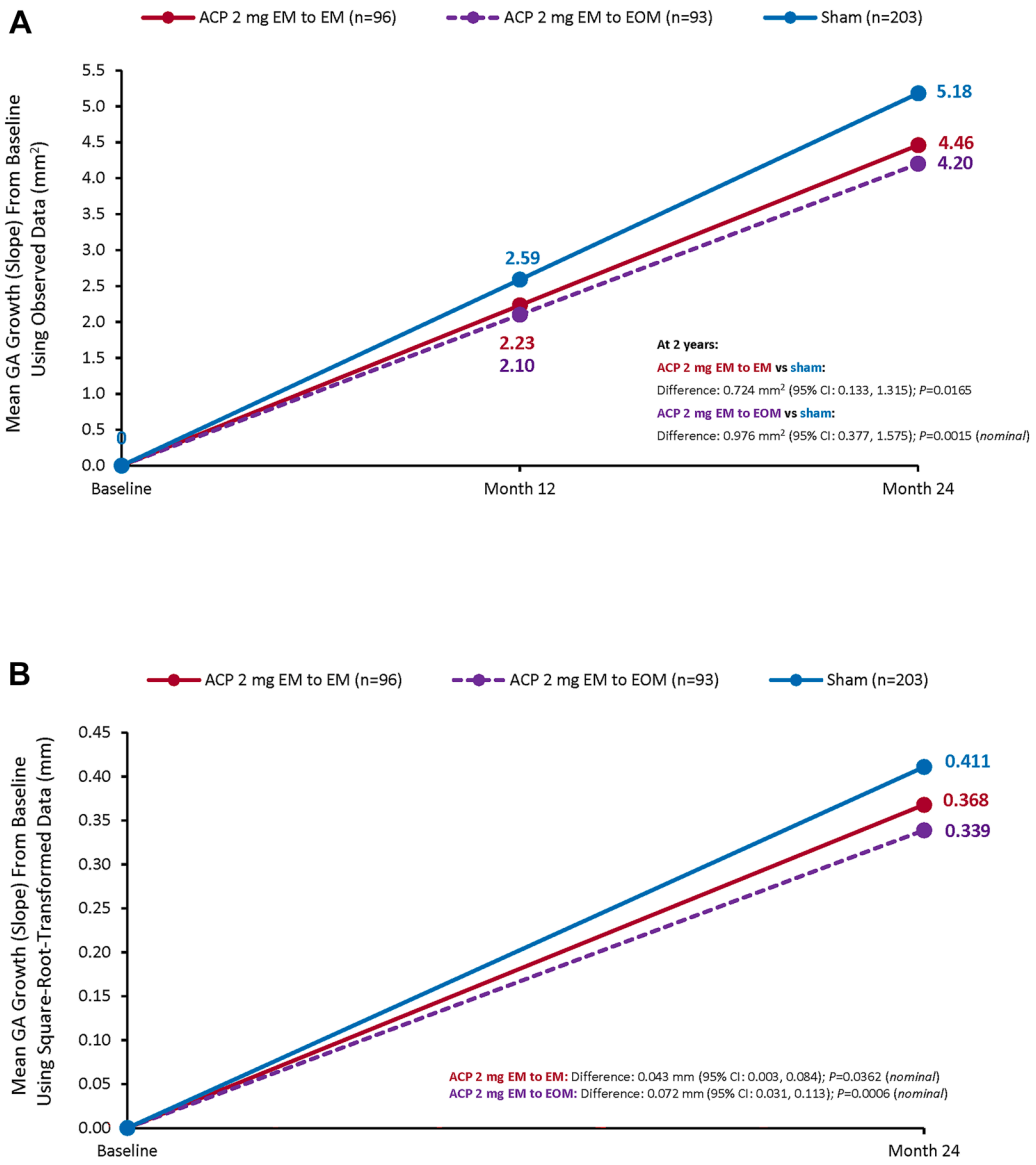

Figure 2. Line graphs showing geographic atrophy (GA) growth over time at year 2 using a slope analysis (re-randomized analysis set): using observed data (**A**) and using square root-transformed data (**B**). This analysis is based on a mixed model assuming constant growth rate from baseline to year 2. The avacincaptad pegol (ACP) 2-mg every other month (EOM) group received monthly ACP 2 mg in the first year (ACP 2 mg every month [EM] to EOM). CI = confidence interval.

hyperemia, cataract, dry eye, eye pain, vitreous detachment, retinal hemorrhage, eye irritation, reduced VA, visual impairment, vision blurred, and vitreous floaters (Table S4, available at www.aaojournal.org). Of note, ACP was administered as an intravitreal injection, whereas the sham procedure involved the blunt opening of an empty, needleless syringe barrel placed on the conjunctiva in the inferotemporal quadrant of the eyeball to simulate the pressure of an injection. Results were similar for the re-randomized analysis set over 2 years (all patients who were randomized again at month 12; Tables S5 and S6, available at www.aaojournal.org). Over 2 years, serious ocular TEAEs in the study eye were reported in 4 eyes (1.8%) with ACP 2 mg and 2 eyes (0.9%) with sham administration. The serious ocular TEAEs with ACP 2 mg included CNV (2 eyes [0.9%]), culture-positive endophthalmitis (1 eye [0.4%]), and subluxated intraocular lens (device dislocation; 1 eye [0.4%]). Both CNV cases occurred in year 1, whereas the culture-positive endophthalmitis and subluxated intraocular lens occurred in year 2; all were with ACP 2 mg EM. The culture-positive endophthalmitis was reported as related to the injection procedure, and 1 case of CNV was reported as related to ACP 2 mg. With sham administration, 1 eye (0.5%) demonstrated CNV and 1 eye (0.5%) demonstrated both reduced VA and reduced VA transiently over 2 years.

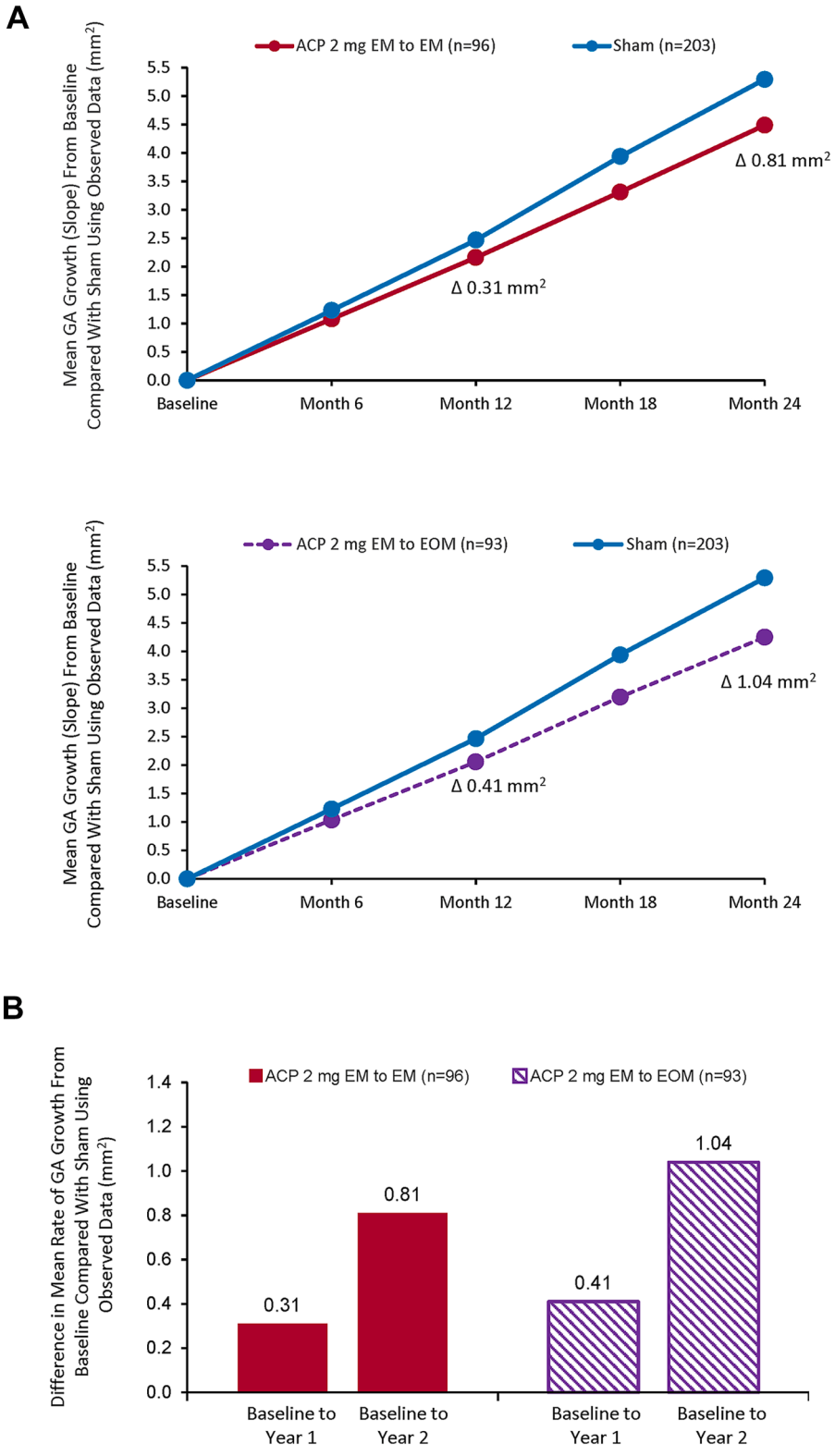

Figure 3. Graphs showing the piecewise analysis of treatment effect over 2 years (re-randomized analysis set): mean geographic atrophy (GA) growth (slope) from baseline for avacincaptad pegol (ACP) 2 mg every month (EM) and every other month (EOM) compared with sham administration (**A**) and difference in mean rate of GA growth from baseline for ACP 2 mg EM and EOM compared with sham administration (**B**). This is a simplified piecewise slope spline multivariable and repeated measures analysis. This analysis is based on a mixed-effects model for repeated measures assuming a piecewise linear growth slope every 6 months. The model included effects for treatment, time, and time-by-treatment interaction. The ACP 2-mg EOM group received monthly ACP 2 mg in the first year (ACP 2 mg EM to EOM).

Table 2. Mean Change in Best-Corrected Visual Acuity and Low-Luminance Best-Corrected Visual Acuity (ETDRS Letters) from Baseline to Year 2 (Intention-to-Treat Analysis Set)

Variable	Least-Squares Mean		Absolute Difference*	95% Confidence Interval	*P* Value (Nominal)
	Avacincaptad Pegol 2 mg (n = 225)	*Sham (n = 222)*			
BCVA	−7.31	−6.48	−0.83	−3.79 to 2.12	0.58
LL BCVA	−10.58	−9.1	−1.49	−4.79 to 1.81	0.38

BCVA = best-corrected visual acuity; LL = low-luminance.
Mixed model for repeated measures analysis. Avacincaptad pegol 2 mg included both every month and every-other-month groups.
*Difference in least-squares mean between groups.

All the serious ocular TEAEs with sham administration occurred in year 1 (Table S7, available at www.aaojournal.org).

Over 2 years, 11 patients (4.9%) with ACP 2 mg and 9 patients (4.1%) with sham administration withdrew from the study because of a TEAE. Four patients experienced ocular TEAEs leading to study drug discontinuation with ACP 2 mg over 2 years: CNV, vitreous detachment, IOP increase, and device dislocation, 2 of which (vitreous detachment and IOP increase) also were related to the injection procedure. No TEAEs leading to study drug discontinuation were related to ACP 2 mg or sham administration over 2 years. Over 2 years, 1 event of intraocular inflammation was reported in an eye that received ACP 2 mg EM in year 2. This was a nonserious event of trace vitreous cells (lasting 13 days), that was moderate in severity and not related to the study drug or the injection procedure. The event resolved, the eye recovered fully with resolution of the cells, and the patient continued in the study with study drug injections after resolution without additional reports of inflammation. No events of ischemic optic neuropathy, retinal vasculitis, or retinal occlusive vasculitis were reported over 2 years in either treatment group (Table 4). A TEAE of increased IOP, which was investigator determined, occurred in 30 eyes (13.3%) with ACP 2 mg and 2 eyes (0.9%) with sham administration over 2 years. Most of these events occurred after injection (84.4%), were transient, and resolved the same day. All but 1 event resolved without sequelae. This event occurred in the ACP 2 mg EM group in a patient with glaucoma and was under control with IOP-lowering medication. A total of 15 patients (6.7%) in the ACP 2 mg group and 13 patients (5.9%) in the sham administration group received IOP-lowering medication over 2 years. Over 2 years, the incidence of CNV in the study eye was 11.6% (n = 26) with ACP 2 mg and 9.0% (n = 20) with sham administration. In year 2, the incidence of CNV in the study eye was 7.3% (n = 7) with ACP 2 mg EM, 4.3% (n = 4) with ACP 2 mg EOM, and 5.4% (n = 11) with sham administration (Table 5).

In the safety analysis set, the incidence of nonocular TEAEs was similar between ACP 2 mg (76.4%) and sham administration (72.1%) over 2 years (Table S8, available at www.aaojournal.org). The incidence of serious nonocular TEAEs also was similar between ACP 2 mg (24.4%) and sham administration (22.1%) over 2 years (Table S9, available at www.aaojournal.org). Results were consistent with the re-randomized analysis set over 2 years (Tables S8 and S9). Over 2 years, 16 deaths occurred, and 9 deaths were the result of TEAEs. Of these, 4 deaths occurred with ACP 2 mg and 5 deaths occurred with sham administration. None of the deaths were related to

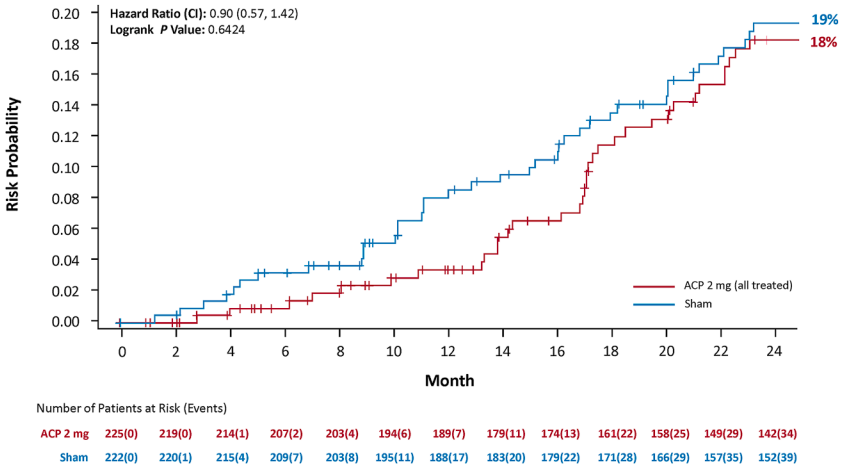

Figure 4. Time-to-event analysis of persistent visual acuity loss of 15 or more ETDRS letters from baseline to year 2 at 2 consecutive visits (intention-to-treat analysis set). ACP = avacincaptad pegol; CI = confidence interval.

Table 3. Summary of Treatment-Emergent Adverse Events over 2 Years (Safety Analysis Set)

Variable	Avacincaptad Pegol 2 mg (n = 225)	Sham (n = 222)
Nonocular TEAEs		
TEAEs	172* (76.4)	160 (72.1)
TEAEs related to injection procedure	2 (0.9)	0 (0)
TEAEs related to study drug	0 (0)	0 (0)
Serious TEAEs	55 (24.4)	49 (22.1)
Severe TEAEs	43 (19.1)	39 (17.6)
TEAEs leading to study drug discontinuation	7 (3.1)	9 (4.1)
Ocular TEAEs		
Ocular TEAEs		
Study eye	144 (64.0)	107 (48.2)
Fellow eye	83 (36.9)	67 (30.2)
Serious ocular TEAEs		
Study eye	4 (1.8)	2 (0.9)
Fellow eye	2 (0.9)	0
Severe ocular TEAEs, study eye	11 (4.9)	2 (0.9)
Ocular TEAEs related to injection procedure, study eye	83 (36.9)	47 (21.2)
Ocular TEAEs related to study drug, study eye	7 (3.1)	2 (0.9)
Ocular TEAEs leading to study drug discontinuation, study eye	4 (1.8)	0

TEAE = treatment-emergent adverse event.
Data are presented as no. (%).

ACP 2 mg, sham administration, or the injection procedure. Over 2 years, no clinically relevant changes in vital signs, laboratory parameters, and electrocardiography findings were noted (data not shown).

Discussion

The 2-year results from GATHER2 demonstrated the continued safety and tolerability of ACP 2 mg, dosed as either ACP 2 mg EM or EOM in year 2. Both doses continued to slow the rate of GA growth versus sham administration. Based on a piecewise analysis, the treatment effect of ACP 2 mg (defined as the difference between sham administration and each respective ACP arm) was observed as early as month 6 and increased over time through 2 years, more than doubling compared with year 1. As expected, no substantial differences were found in mean change in BCVA or LL BCVA from baseline to year 2, which were similar to results for year 1.[15]

As demonstrated by the 2-year data for ACP 2 mg EM and EOM dosing, patients randomized again to ACP 2 mg EOM, who received fewer injections of ACP 2 mg, did not seem to have worse outcomes than patients randomized again to ACP 2 mg EM compared with those receiving sham administration. It should be noted that although this study was not powered to compare the 2 re-randomized ACP 2 mg regimens with one another at the end of year 2, the slight numerical variations in efficacy results between ACP 2 mg EM and ACP 2 mg EOM likely are not the result of demographic differences. Key baseline demographics and clinical characteristics seemed to be balanced in the re-randomized group, with small numerical differences in some demographic characteristics such as sex (10.5% difference) and age (difference of 1.6 years), which are not considered confounders to GA growth.[20] The possibility cannot be dismissed entirely that other baseline characteristics (not accounted for in the clinical program) might have influenced the slight difference in GA growth rates between ACP 2 mg EM and ACP 2 mg EOM.

Table 4. Adverse Events of Special Interest in the Study Eye

	Year 1		Year 2			Over 2 Years	
Variable	*Avacincaptad Pegol 2 mg (n = 225)*	*Sham (n = 222)*	*Avacincaptad Pegol 2 mg Every Month to Every Month (n = 96)*	*Avacincaptad Pegol 2 mg Every Month to Every Other Month (n = 93)*	*Sham (n = 203)*	*Avacincaptad Pegol 2 mg (n = 225)*	*Sham (n = 222)*
Intraocular inflammation	0	0	1 (1.0)	0	0	1 (0.4)	0
Culture-positive endophthalmitis	0	0	1 (1.0)	0	0	1 (0.4)	0
Ischemic optic neuropathy	0	0	0	0	0	0	0
Retinal vasculitis	0	0	0	0	0	0	0

Year 1 and over 2 years are based on the safety analysis set. Year 2 is based on the re-randomized analysis set. Data are presented as no. (%).

Table 5. Choroidal Neovascularization in the Study Eye

Variable	Year 1		Year 2			Over 2 Years	
	Avacincaptad Pegol 2 mg (n = 225)	*Sham (n = 222)*	*Avacincaptad Pegol 2 mg Every Month to Every Month (n = 96)*	*Avacincaptad Pegol 2 mg Every Month to Every Other Month (n = 93)*	*Sham (n = 203)*	*Avacincaptad Pegol 2 mg (n = 225)*	*Sham (n = 222)*
Choroidal neovascularization, no. (%)	15 (6.7)	9 (4.1)	7 (7.3)	4 (4.3)	11 (5.4)	26 (11.6)	20 (9.0)

Year 1 and over 2 years are based on the safety analysis set. Year 2 is based on the re-randomized analysis set.

However, it can be concluded from the results that a consistent reduction in GA growth was observed with ACP 2 mg EM and ACP 2 mg EOM compared with sham administration at 2 years. These data suggest that after 1 year of ACP 2 mg EM treatment, a less frequent dosing regimen may be sufficient to maintain effective inhibition of C5 and to ensure continued slowing of GA area growth.

Although BCVA is an important measurement tool to assess changes in VA over time, substantial differences between treatment and sham administration are difficult to demonstrate within the time frame of a 2-year clinical trial in eyes with GA. Nonetheless, at various time points in the study, patients can experience a significant and permanent drop in VA. Therefore, it is more appropriate to analyze VA data by using the time-to-event analysis to characterize VA loss better. In year 1, an exploratory time-to-event analysis evaluated the persistent loss of 15 or more letters from baseline to year 1, which signaled that the rate of persistent VA loss with ACP 2 mg EM versus sham administration was more than halved (HR, 0.41).[15] This observation also was corroborated by a post hoc analysis of pooled 1-year data from GATHER1 and GATHER2 that showed the risk of progression to persistent VA loss was delayed with ACP 2 mg treatment based on several categorical outcome measures.[21] Over 2 years, reducing the risk of persistent VA loss of 15 or more letters with ACP 2 mg compared with sham administration did not reach statistical significance. The year 1 analysis was post hoc and included eyes that received monthly ACP 2 mg and sham administration from the full ITT analysis set (n = 225 and n = 222, respectively).[15] In year 2, this analysis was prespecified and included eyes from the re-randomized analysis set that received both ACP 2 mg EM and EOM compared with monthly sham administration, respectively. Of note, in the exploratory analysis of persistent VA loss of 20 or more letters, a larger separation between ACP 2 mg and sham administration was observed. Furthermore, these results also highlighted the challenges in determining how best to measure changes in vision in a clinical trial of patients with GA. In particular, it demonstrated how a structural end point of GA lesion growth is a more suitable primary end point because it can be measured accurately in an objective and reproducible manner compared with a functional end point of vision, which is more variable because of factors like lesion location, patient-associated subjectivity, amount of foveal encroachment, and differences in growth rates for peripheral and central disease.

Important differences in study design exist between year 1 and year 2. In year 1, the primary end point was analyzed using a slope analysis of square root-transformed data to determine the mean rate of GA growth from baseline to year 1. A post hoc analysis later analyzed the primary end point using a slope analysis of observed data.[15] In year 1 of GATHER2, the mean GA growth (slope) analysis showed similar results using both the square root-transformation and non−square root-transformation, or observed, methods. Hence, the year 2 analysis was performed via the observed or non−square root-transformed method, because this may be easier for clinicians and patients to understand and contextualize because it reflects actual changes in GA size over time. This direct interpretation can be crucial for clinical decision-making and patient communication. Similar to year 1, the mean GA growth (slope) analysis showed similar results using both the square root-transformed and observed data over 2 years. The year 2 analysis of GA lesion growth also was performed on a different study population than year 1. In year 1, all patients received either ACP 2 mg EM or sham administration and constituted the ITT analysis set. The primary analysis was based on an MMRM assuming constant growth rate from baseline to year 1.[15] In year 2, patients received ACP 2 mg EM, ACP 2 mg EOM, or sham administration, constituting the re-randomized analysis set, which is a subset of the year 1 study population who made it to at least the month 12 visit. The primary analysis was based on an MMRM analysis assuming constant growth rate from baseline to year 2. Another important difference was the prespecified hierarchical testing procedure. Both ACP 2 mg EM and ACP 2 mg EOM treatment reduced GA growth versus sham administration over 2 years. The reduction with ACP 2 mg EM versus sham administration was statistically significant; however, no formal statistical test was performed for ACP 2 mg EOM versus sham administration because no statistically significant difference was present in the measure of 15 or more-letter persistent VA loss in the statistical testing sequence before ACP 2 mg EOM versus sham administration for GA growth. Unique to year 2 of GATHER2 was the piecewise analysis of treatment effect of the re-randomized analysis set. This analysis was based on an MMRM analysis assuming a piecewise linear growth slope in 6-month

segments, rather than a constant slope over 2 years, as in the primary year 2 analysis. Based on this piecewise analysis, the treatment effect of ACP 2 mg was observed as early as month 6 and increased over time through 2 years, more than doubling compared with year 1.

The overall safety profile of ACP 2 mg reported through year 2 was consistent with the safety profile established in year 1, and no new safety signals were identified in year 2 or with flexible dosing.[15] ACP 2 mg was well tolerated over 2 years, with few AEs of special interest: 1 case of nonserious intraocular inflammation, 1 case of culture-positive endophthalmitis, and no cases of ischemic optic neuropathy or retinal vasculitis. The incidence of serious ocular TEAEs was low in year 2, with the emergence of 1 case of subluxated intraocular lens and 1 case of culture-positive endophthalmitis with ACP 2 mg EM. The increased incidence of increased IOP is expected with ACP 2 mg because of the intraocular injection volume of 100 µl. The assessment of severity and seriousness for any AE is evaluated by the reporting investigator and must fulfill prespecified criteria. Overall, serious ocular TEAEs over 2 years were low and comparable between the ACP 2-mg and sham groups (1.8% vs. 0.9%, respectively). Over 2 years, a slightly higher percentage of eyes treated with ACP 2 mg (11.6%) demonstrated CNV compared with sham administration (9.0%), which was consistent with year 1. Notably, the incidence of CNV was similar between ACP 2 mg EOM (4.3%) and sham administration (5.4%) in year 2, and the incidence of CNV with ACP 2 mg EM in year 2 (7.3%) was similar to that of ACP 2 mg (overall) in year 1 (6.7%). Based on a post hoc assessment in patients who demonstrated CNV, mean BCVA at year 2 was 58.2 ETDRS letters (95% CI, 48.86−67.47 ETDRS letters) for ACP 2 mg and 63.1 ETDRS letters (95% CI, 54.45−71.66 ETDRS letters) for sham administration ($P = 0.4378$). Accounting for baseline BCVA for ACP 2 mg (72.7 letters) and sham administration (73.9 letters) in patients who demonstrated CNV, this reflects a difference of 3.17 letters (95% CI, −8.1393 to 14.4902 letters; $P = 0.5740$) between ACP 2-mg and sham administration at year 2; however, this post hoc assessment was underpowered.[22,23] Further investigation of this subgroup analysis in a small population of patients who demonstrated macular neovascularization will be detailed in a forthcoming report. It is well recognized that both GA and CNV are part of the AMD spectrum and can occur in the same eye with no exclusive dichotomy.[24−26] According to an Age-Related Eye Disease Study 2 publication, 14% of eyes with GA from a prospective cohort study within a clinical trial demonstrated neovascular AMD over 2 years, which increased to 29% over 4 years.[27]

This study has limitations. Similar to year 1, the patient population is limited to those without foveal center point-involved GA at the time of enrollment, although most of the lesions were less than 500 µm from the foveal center point. Additionally, the observed treatment effect of ACP 2 mg was robust based on sensitivity analyses and consistent across all exploratory prespecified patient subgroups, suggesting that the results can be generalized. The subgroup findings were prespecified as exploratory and were not adjusted for multiplicity; therefore, interpretations are hypothesis generating. Although the 2-year study length can be considered short for a disease with a relatively slow chronic progression, an open-label extension study is ongoing for 18 months that is expected to be complete in 2025 (ClinicalTrials.gov identifier, NCT05536297).

In conclusion, the 2-year data from the GATHER2 trial demonstrate the long-term efficacy and safety of complement C5 inhibition with ACP 2 mg compared with sham administration. Although this study was not designed or powered to compare ACP 2 mg EOM versus EM and no formal test was performed, both ACP 2 mg EM and EOM were effective at slowing the progression of disease relative to sham administration.

Acknowledgments

The authors thank all the GATHER2 program investigators, research staff, and patients at all the clinical sites; Professor Ramin Tadayoni (Université Paris Cité, Ophthalmology Department, AP-HP, Lariboisière, Saint Louis and Fondation Adolphe de Rothschild Hospitals, Paris, France) for his contributions. Medical writing and editorial support were provided by Veronika Khariv, PhD, CMPP, from IMPRINT Science and were funded by Astellas Pharma Inc.

Footnotes and Disclosures

Originally received: September 9, 2024.
Final revision: November 7, 2025.
Accepted: December 8, 2025.
Available online: December 15, 2025. Manuscript no. OPHTHA-D-24-01926.

[1] Sierra Eye Associates, Reno, Nevada.

[2] University of Nevada, Reno School of Medicine, Reno, Nevada.

[3] Department of Surgery, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida.

[4] Ophthalmic Consultants of Boston, Boston, Massachusetts.

[5] Department of Ophthalmology, Duke University, Durham, North Carolina.

[6] Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

[7] New England Retina Consultants, Springfield, Massachusetts.

[8] West Texas Retina Consultants, Abilene, Texas.

[9] Department of Ophthalmology, Baylor College of Medicine, Houston, Texas.

[10] Astellas Pharma Inc., Northbrook, Illinois.

[11] Department of Ophthalmology, University of Bonn, Bonn, Germany.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

A.M.K.: Consultant − AbbVie, Adverum Biotechnologies, Alcon, Annexin Pharmaceuticals, Annexon Biosciences, Apellis Pharmaceuticals, Astellas Pharma Inc., Aviceda Therapeutics, Beacon Therapeutics, Boehringer Ingelheim, Clearside Biomedical, Complement Therapeutics, Exegenesis Bio, EyePoint Pharmaceuticals, 4DMT, Frontera Therapeutics,

Genentech, Gyroscope Therapeutics, i-Lumen Scientific, Janssen Pharmaceuticals, Kodiak Sciences, Kriya Therapeutics, Nanoscope Therapeutics, Novartis, Ocular Therapeutix, Oculis, Ocuphire Pharma, OcuTerra Therapeutics, Olive BioPharma, Opthea, Oxular, Oxurion, Perfuse Therapeutics, Ray Therapeutics, RecensMedical, Regeneron Pharmaceuticals, Regenxbio, ReVive Biotechnology, RevOpsis, Roche, Sanofi, Stealth BioTherapeutics, Thea Pharma, Unity Biotechnology, Vanotech, Vial; Financial support – Adverum, Alexion, Annexon, Apellis Pharmaceuticals, Astellas Pharma Inc., Aviceda Therapeutics, Exegenesis, EyePoint, 4DMT, Genentech, Gyroscope, Janssen, Kodiak, Neurotech Pharmaceuticals, Ocular Therapeutix, Oculis, OcuTerra, Opthea, Oxular, Oxurion, Regenxbio, Roche, Vanotech, Unity Biotechnology; Lecturer – Astellas Pharma Inc.; Equity owner – Aviceda Therapeutics, Oculis, Opthea, Perfuse Therapeutics, PolyPhotonix, RecensMedical, RevOpsis, Vial; Board of directors – Oculis

C.J.D.: Consultant – 4DMT, AbbVie, Adverum, Alimera Sciences, Apellis, Astellas Pharma Inc., Beacon, Cognition, EyeBio, EyePoint, Galimedix Therapeutics, Genentech, Kodiak, Ocuphire, Ocular Therapeutix, OcuCool, Oculis, Opthea, Regeneron, Regenxbio, Roche, Samsung Bioepsis, Sanofi, Unity; Financial support – Adverum, Alexion, Annexon, Astellas Pharma Inc., Aviceda, Bayer, Boehringer Ingelheim, Cognition Therapeutics, Curacle, EyeBio, 4DMT, Genentech, Gyroscope, Kodiak, Novartis, Oculis, Ocular Therapeutix, Regeneron, Regenxbio, Rezolute, Roche, Unity; Lecturer – Astellas Pharma Inc., Genentech

J.S.H.: Consultant – AbbVie/Regenxbio, Abpro, Adverum, AffaMed Therapeutics, Akouos, Alimera, Allgenesis Biotherapeutics, Alzheon, Annexon, Apellis, AsclepiX Therapeutics, Astellas Pharma Inc., Aviceda, Bausch + Lomb, Beacon, Bionic Vision Technologies, Biovisics, Caeregen Therapeutics, Cognition, Curacle, Daiichi Sankyo, Frontera, Galimedix, Genentech/Roche, Immunogen, Janssen R&D, jCyte, Kriya, Manistee, Nanoscope, NGM Biopharmaceuticals, Notal Vision, Novartis, Ocular Therapeutix, Ocuphire, OcuTerra, Opthea, Ora, Inc., Osanni Bio, Perceive Biotherapeutics, Ray Therapeutics, Regeneron Pharmaceuticals, Inc., RevOpsis, Sanofi, Skyline, Thea Therapeutics, Tilak Healthcare, Unity Bio, Vanotech, Visgenx, Xequel Bio; Chief scientific officer – Ocular; Financial support – 4DMT, AbbVie/Regenxbio, Annexon, Apellis, Ashvattha Therapeutics, Astellas Pharma Inc., Beacon Therapeutics, Cognition, Curacle, Genentech/Roche, Janssen R&D, Notal Vision, Novartis, Oculis, OcuTerra, Opthea, Perceive Bio, Skyline Therapeutics, Stealth BioTherapeutics, Vanotech; Equity owner – Adverum, Aldeyra Therapeutics, Alzheon, Aviceda, Caeregen, jCyte, Manistee, Ocuphire, Ocular Therapeutix, Osanni Bio, Ray, RevOpsis, Vinci Pharmaceuticals, Visgenx, Vitranu; Leadership role – Ocular Therapeutix

G.J.J.: Consultant – Adverum, Annexon, Astellas Pharma Inc., Bausch + Lomb, BlueRock Therapeutics, Boehringer Ingelheim, Editas Medicine, EyePoint, 4DMT, Implicit Bioscience, Kriya Therapeutics, LumiThera, Neurotech, Novartis, Ocular Therapeutix, Outlook Therapeutics, Regeneron, Ripple Therapeutics, Roche/Genentech

P.K.K.: Consultant – Alkeus, AffaMed, Allergan/AbbVie, Allgenesis, Alnylam Pharmaceuticals, Alzheon, Annexon, AsclepiX, Astellas Pharma Inc., Aviceda, Bausch + Lomb, Bayer, Biogen, Bionic Vision Technologies, Boehringer Ingelheim, Chengdu Kanghong Pharmaceutical Group, Clearside, Coherus BioSciences, Complement Therapeutics, DelSiTech, Dompé, Duet BioTherapeutics, Frontera, Galecto Biotech, Galimedix, Genentech/Roche, Glaukos, Innovent Biologics, iRenix Medical, jCyte, Kanaph Therapeutics, Kera Therapeutics, Kriya, Nanoscope, Novartis, Ocugenix, Oculis, Omeros, Opthea, Palatin Technologies, Regeneron, Regenxbio, Resonance Medicine, RetinAI, Retinal Sciences, Roivant Sciences, Samsung Bioepis, SGN Nanopharma, Stealth, Stuart Therapeutics, Sustained Nano Systems, Takeda, Théa Pharma, 20/20 Onsite, Vanotech, Carl Zeiss Meditec; Employee and Leadership role – Ocular Therapeutix

D.R.L.: Consultant – Annexon Biosciences; Apellis Pharmaceuticals, Stealth BioTherapeutics; Grants – Alexion Pharmaceuticals, Annexon Biosciences, Apellis Pharmaceuticals, Aviceda Therapeutics, Stealth BioTherapeutics; Scientific Advisory Board – Stealth BioTherapeutics; Trial Steering Committee – Annexon Biosciences and Astellas Pharma Inc.

S.S.P.: Consultant – AiViva BioPharma, Allergan, Allgenesis, Genentech-Roche, Kala Pharmaceuticals, Kodiak, Ocugenix, Regenxbio; Advisory board member – Allergan, Allgenesis, Astellas Pharma Inc., Genentech-Roche, Kodiak; Financial support – Aerie, Aerpio, Allergan, Allgenesis, Apellis, Astellas Pharma Inc., Boehringer Ingelheim, Chengdu Kanghong, Clearside, EyePoint, Genentech-Roche, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Kodiak Sciences, Mylan, Novartis, Oculis, Opthea, OraPharma, Oxurion, Regeneron, Samsung, Smilebiotek Zhuhai, Stealth BioTherapeutics, ThromboGenics, Xbrane Biopharma; Equity owner – Allgenesis, Aviceda

L.V.: Consultant – AbbVie/Allergan, Alcon, Alimera Sciences, Apellis Pharmaceuticals, Astellas Pharma Inc., Bausch + Lomb, BioCryst, BVI, BMC, Clearside Biomedical, Coherus BioSciences, DORC, Guidepoint, Gyroscope Therapeutics, Janssen/Johnson & Johnson, Lexitas, Nanoscope, Novartis, Ocugen, Ocular Therapeutix, Ocular Surgical, OcuTerra Therapeutics, ONL Therapeutics, Outlook Therapeutics, Regenxbio, Roche/Genentech; Financial support – AbbVie/Allergan, AGTC, Alcon, Aldeyra Therapeutics, Apellis, Gyroscope, Heidelberg Engineering, Janssen/Johnson & Johnson, National Eye Institute, Novartis, Ocugen, Optos, Regenxbio, Roche/Genentech

C.Y.W.: Consultant – Alcon, Alimera, Allergan/AbbVie, Apellis, Astellas Pharma Inc., DORC, EyePoint, Genentech, Opthea, Regeneron, Regenxbio, Zeiss; Financial support – DRCR Retina Network, AGTC, Alimera Sciences; Royalties – Springer Publishing; Leadership positions – American Society of Cataract and Refractive Surgery, American Society of Retina Specialists, Retina Society, Women in Ophthalmology

H.P.: Employee (former) – Astellas Pharma Inc.

J.C.: Employee – Astellas Pharma Inc. (former), 4D Molecular Therapeutics; Equity owner – Adverum, Astellas Pharma Inc., Opthea, 4D Molecular Therapeutics

D.D.: Employee (former) – Astellas Pharma Inc.

D.L.: Employee – Astellas Pharma Inc.

E.H.: Employee (former) – Astellas Pharma Inc.

F.G.H.: Consultant – AbbVie, Acucela, Alcon, Alexion, Alnylam, Annexon, Apellis, Astellas Pharma Inc., Bayer, Biogen, Boehringer Ingelheim, Cirrus, EyePoint, Galimedix, Genentech/Roche, Graybug Vision, Heidelberg Engineering, Lin Bioscience, Janssen, Merck, Novartis, Oculis, Okuvision, Opthea, Oxurion, RetinAI, Sanofi, Science, Stealth BioTherapeutics, TenPoint, Topcon, Zeiss. Financial support – AbbVie, Acucela, Allergan, Annexon, Apellis, Astellas Pharma Inc., Bayer, Bioeq, CenterVue, Geuder, Genentech/Roche, Heidelberg Engineering, NightStar, Novartis, Science, Zeiss, 4D Molecular Therapeutics.

This study was funded by Astellas Pharma Inc. Astellas participated in the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, preparation, and review and approval of the manuscript. The Article Publishing Charge (APC) for this article was paid by Astellas.

Data Sharing Statement: Details for how researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials can be found at https://www.clinicaltrials.astellas.com/transparency.

*A list of Members of the GATHER2 Trial Investigators is available at www.aaojournal.org.

Presented at: The American Academy of Ophthalmology Annual Meeting, November 2023, San Francisco, California; the FLORetina Meeting, December 2024, Florence, Italy; the Hawaiian Eye and Retina Annual Meeting, January 2024, Wailea, Hawaii; the Angiogenesis, Exudation, and Degeneration Meeting, February 2024, virtual; the Macula Society Annual

Meeting, February 2024, Palm Springs, California; the Sonoma Eye Meeting, March 2024, Sonoma, California; the Retina World Congress, May 2024, Fort Lauderdale, Florida; the 36th International Congress of German Ophthalmic Surgery, June 2024, Nuremberg, Germany; the 117th Swiss Ophthalmological Society Annual Congress, August 2024, St. Gallen, Switzerland; and the European Society of Retina Specialists Congress, September 2024, Barcelona, Spain.

HUMAN SUBJECTS: Human subjects were included in this study. In brief, GATHER2 enrolled patients from 205 sites in 20 countries and was conducted in full compliance with the principles of the Declaration of Helsinki and in compliance with the respective law and regulations of the country in which the study was conducted (list of IRBs is available at www.aaojournal.org). The clinical study protocol, any amendments, and the patient informed consent provisions were reviewed and approved by the appropriate Independent Ethics Committee or Institutional Review Board for each center involved in the study, according to national or local regulations and in accordance with the FDA Title 21, Code of Federal Regulations Parts 56.107 through 56.115 and the ICH-GCP guidelines (Committee for Proprietary Medicinal Products/ICH/135/95).

No animal subjects were included in this study.

Author Contributions:

Conception and design: Khanani, Danzig, Heier, Jaffe, Kaiser, Lally, Patel, Clark, Desai, Holz

Analysis and interpretation: Khanani, Danzig, Heier, Jaffe, Kaiser, Lally, Vajzovic, Weng, Patel, Clark, Desai, Luo, Henry, Holz

Data collection: Khanani, Danzig, Heier, Lally, Patel, Patel, Clark, Holz

Obtained funding: N/A

Overall responsibility: Khanani, Danzig, Heier, Jaffe, Kaiser, Lally, Patel, Vajzovic, Weng, Patel, Clark, Desai, Luo, Henry, Holz

Abbreviations and Acronyms:
ACP = avacincaptad pegol; **AE** = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CNV** = choroidal neovascularization; **EM** = every month; **EOM** = every other month; **FAF** = fundus autofluorescence; **FDA** = Food and Drug Administration; **GA** = geographic atrophy; **HR** = hazard ratio; **IOP** = intraocular pressure; **ITT** = intention-to-treat; **LL** = low-luminance; **MMRM** = mixed model for repeated measures; **SD** = standard deviation; **SE** = standard error; **TEAE** = treatment-emergent adverse event; **VA** = visual acuity.

Keywords:
Age-related macular degeneration, Avacincaptad pegol, C5 inhibitor, Complement, Geographic atrophy.

Correspondence:
Arshad M. Khanani, MD, Sierra Eye Associates, 950 Ryland Street, Reno, NV 89502. E-mail: arshad.khanani@gmail.com.

References

1. Fleckenstein M, Keenan TDL, Guymer RH, et al. Age-related macular degeneration. *Nat Rev Dis Primers*. 2021;7(1):31.
2. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(3):369−390.
3. Caswell D, Caswell W, Carlton J. Seeing beyond anatomy: quality of life with geographic atrophy. *Ophthalmol Ther*. 2021;10(3):367−382.
4. Carlton J, Barnes S, Haywood A. Patient perspectives in geographic atrophy (GA): exploratory qualitative research to understand the impact of GA for patients and their families. *Br Ir Orthopt J*. 2019;15(1):133−141.
5. Patel PJ, Ziemssen F, Ng E, et al. Burden of illness in geographic atrophy: a study of vision-related quality of life and health care resource use. *Clin Ophthalmol*. 2020;14:15−28.
6. Toomey CB, Johnson LV, Bowes Rickman C. Complement factor H in AMD: bridging genetic associations and pathobiology. *Prog Retin Eye Res*. 2018;62:38−57.
7. Sofat R, Casas JP, Webster AR, et al. Complement factor H genetic variant and age-related macular degeneration: effect size, modifiers and relationship to disease subtype. *Int J Epidemiol*. 2012;41(1):250−262.
8. Seth A, Cui J, To E, et al. Complement-associated deposits in the human retina. *Invest Ophthalmol Vis Sci*. 2008;49(2):743−750.
9. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2005;102(20):7227−7232.
10. Johnson LV, Ozaki S, Staples MK, et al. A potential role for immune complex pathogenesis in drusen formation. *Exp Eye Res*. 2000;70(4):441−449.
11. Loyet KM, Deforge LE, Katschke Jr KJ, et al. Activation of the alternative complement pathway in vitreous is controlled by genetics in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2012;53(10):6628−6637.
12. Apellis Pharmaceuticals, Inc. Syfovre® [package insert]. *Apellis Pharmaceuticals*. Inc; 2024.
13. Astellas Pharma US, Inc. IzervayTM [package insert]. *Astellas Pharma US*. Inc; 2025.
14. Khan H, Aziz AA, Sulahria H, et al. Emerging treatment options for geographic atrophy (GA) secondary to age-related macular degeneration. *Clin Ophthalmol*. 2023;17:321−327.
15. Khanani AM, Patel SS, Staurenghi G, 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(10411):1449−1458.
16. Jaffe GJ, Westby K, Csaky KG, 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.
17. Borchert GA, Shamsnajafabadi H, Hu ML, et al. The role of inflammation in age-related macular degeneration-therapeutic landscapes in geographic atrophy. *Cells*. 2023;12(16):2092.
18. Patel SS, Lally DR, Hsu J, et al. Avacincaptad pegol for geographic atrophy secondary to age-related macular degeneration: 18-month findings from the GATHER1 trial. *Eye (Lond)*. 2023;37(17):3551−3557.
19. Li AS, Myers J, Stinnett SS, et al. Gradeability and reproducibility of geographic atrophy measurement in GATHER-1, a phase II/III randomized interventional trial. *Ophthalmol Sci*. 2024;4(2):100383.

20. Grassmann F, Fleckenstein M, Chew EY, et al. Clinical and genetic factors associated with progression of geographic atrophy lesions in age-related macular degeneration. *PLoS One*. 2015;10(5):e0126636.
21. Danzig CJ, Khanani AM, Kaiser PK, 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.
22. Heier JS, Lad EM, Holz FG, 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. *Lancet*. 2023;402(10411):1434−1448.
23. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127(2):186−195.
24. Blodi BA, Domalpally A, Corkery E, et al. Prevalence of macular atrophy in the MARINA study of ranibizumab versus sham for neovascular age-related macular degeneration. *Ophthalmol Retina*. 2023;7(8):661−671.
25. Sunness JS, Gonzalez-Baron J, Bressler NM, et al. The development of choroidal neovascularization in eyes with the geographic atrophy form of age-related macular degeneration. *Ophthalmology*. 1999;106(5):910−919.
26. Rahimy E, Khan MA, Ho AC, et al. Progression of geographic atrophy: retrospective analysis of patients from the IRIS® Registry (Intelligent Research in Sight). *Ophthalmol Sci*. 2023;3(4):100318.
27. Keenan TD, Agrón E, Domalpally A, et al. Progression of geographic atrophy in age-related macular degeneration: AREDS2 report number 16. *Ophthalmology*. 2018;125(12):1913−1928.