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Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration

A Randomized Phase 2 Trial

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Purpose: Geographic atrophy (GA), a late stage of age-related macular degeneration (AMD), is a major cause of blindness. Even while central visual acuity remains relatively well preserved, GA often causes considerable compromise of visual function and quality of life. No treatment currently exists. We evaluated the safety and efficacy of pegcetacoplan, a complement C3 inhibitor, for treatment of GA.

Design: Prospective, multicenter, randomized, sham-controlled phase 2 study.

Participants: Two hundred forty-six patients with GA.

Methods: Patients with GA were assigned randomly in a 2:2:1:1 ratio to receive intravitreal injections of 15 mg pegcetacoplan monthly or every other month (EOM) or sham intravitreal injections monthly or EOM for 12 months with follow-up at months 15 and 18. Area and growth of GA were measured using fundus autofluorescence imaging.

Main Outcome Measures: The primary efficacy end point was mean change in square root GA lesion area from baseline to month 12. Secondary outcome measures included mean change from baseline in GA lesion area without the square root transformation, distance of GA lesion from the fovea, best-corrected visual acuity (BCVA), low-luminance BCVA, and low-luminance visual acuity deficit. The primary safety end point was the number and severity of treatment-emergent adverse events.

Results: In patients receiving pegcetacoplan monthly or EOM, the GA growth rate was reduced by 29% (95% confidence interval [CI], 9–49; $P = 0.008$) and 20% (95% CI, 0–40; $P = 0.067$) compared with the sham treatment group. Post hoc analysis showed that the effect was greater in the second 6 months of treatment, with observed reductions of 45% ($P = 0.0004$) and 33% ($P = 0.009$) for pegcetacoplan monthly and EOM, respectively. Two cases of culture-positive endophthalmitis and 1 case of culture-negative endophthalmitis occurred in the pegcetacoplan monthly group. New-onset investigator-determined exudative AMD was reported more frequently in pegcetacoplan-treated eyes (18/86 eyes [20.9%] and 7/79 eyes [8.9%] in monthly and EOM groups, respectively) than in sham-treated eyes (1/81 eyes [1.2%]).

Conclusions: Local C3 inhibition with pegcetacoplan resulted in statistically significant reductions in the growth of GA compared with sham treatment. Phase 3 studies will define the efficacy and safety profile further. *Ophthalmology 2020;127:186-195 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

See Commentary on page 196.

Geographic atrophy (GA) is a late stage of age-related macular degeneration (AMD), a chronic disease of the retina and a major cause of irreversible blindness.[1] In the United States, GA affects nearly 1 million people and accounts for approximately one quarter of cases of legal blindness.[2,3] Vision loss associated with GA causes difficulty with reading and driving and significantly affects quality of life.[2,4] The disease is characterized by loss of retinal pigment epithelium, photoreceptors, and underlying choriocapillaris.[5] Areas of atrophy enlarge and may

https://doi.org/10.1016/j.ophtha.2019.07.011
ISSN 0161-6420/19

coalesce, leading to irreversible loss of central vision. Even while visual acuity remains relatively well preserved, GA often causes considerable compromise of visual function as a result of parafoveal scotomas and foveal function abnormalities.[6] Approximately 50% of patients with unilateral GA demonstrate bilateral GA within 7 years of diagnosis.[7] Geographic atrophy also is common in patients with neovascular AMD, the other form of late AMD.[8,9] Although neovascular AMD usually can be treated effectively with vascular endothelial growth factor (VEGF) inhibitors, patients frequently demonstrate GA within 5 years of starting therapy.[10] There are no approved treatments for GA.

The complement system plays critical roles in both innate and adaptive immunity, contributing to immune surveillance, inflammation, and homeostasis via 3 different activation pathways (classical, alternative, and lectin) and numerous effector molecules.[11] Its diverse functions include recruitment and activation of immune cells, opsonization of pathogens to target them for phagocytosis, and direct destruction of pathogens by the membrane attack complex. Under normal conditions, mammalian complement is tightly regulated to avoid damage to host cells. Dysregulation of the complement system seems to be a major contributor to the pathogenesis of AMD. Genetic variants of complement *C3*—the central component of all 3 complement activation pathways—and variants of *CFH*, *CFI*, and *CFB*—factors that affect C3 activation or degradation of its active fragments—are associated strongly with increased risk of both the exudative and atrophic forms of AMD.[12,13] Complement activation products have been identified at elevated levels in plasma of AMD patients and locally deposited in ocular tissues, most notably in drusen.[14–17] Moreover, oxidative stress has been linked to AMD through formation of neoepitopes that bind to autoantibodies capable of activating complement.[18–20]

Despite considerable investigation,[19,21–25] understanding of how different complement activation pathways and effectors contribute to development and progression of AMD remains incomplete. Given the potential involvement of multiple pathways and effectors, C3 is an attractive target in AMD because it is the point of convergence for all 3 activation pathways and is upstream of all major effectors. The Filly phase 2 trial (ClinicalTrials.gov identifier NCT02503332) was conducted to evaluate the safety, tolerability, and efficacy of intravitreally administered pegcetacoplan, a pegylated complement C3 inhibitor peptide, given monthly or every other month (EOM) to patients with GA secondary to AMD.

Methods

Study Design

The 18-month prospective, multicenter, randomized, sham-controlled phase 2 study enrolled patients at 46 sites in the United States (New England Institutional Review Board, University of Miami, Mayo Clinic, Institutional Review Board of the Cleveland Clinic Foundation, Duke University Health System Institutional Review Board, and Research Compliance Office, Stanford University), Australia (Bellberry Ltd), and New Zealand (Northern A Health and Disability Ethics Committee, Health and Disability Ethics Committees, and Ministry of Health). The study was performed in accordance with the tenets of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and all applicable regulations. Institutional review board or ethics committee approval was obtained at each site. All patients provided written informed consent.

Eligible patients were randomized in a 2:2:1:1 ratio to receive 15 mg pegcetacoplan monthly, 15 mg pegcetacoplan EOM, sham injection monthly, or sham injection EOM for 12 months (Fig 1). Randomization was performed using a web-based system, and the randomization schedule was blocked to ensure balanced treatment allocations within sites. Pegcetacoplan was administered by intravitreal injection in a 100-μl volume using a thin-walled needle of either 27 gauge or 29 gauge. Patients returned to the study site to be assessed for acute safety 7 days after the first injection. Thereafter, patients received additional pegcetacoplan (or sham) injections monthly or EOM through month 12 and returned at months 15 and 18 for safety and efficacy follow-up. Patients who discontinued treatment could remain in the study and receive scheduled study procedures (except pegcetacoplan or sham injection). Patients, study personnel responsible for performing imaging and visual acuity assessments, and reading center personnel were masked to treatment assignment. The sponsor, physicians administering injections and assessing adverse events, and other study personnel not involved in efficacy assessments were not masked.

The sponsor, Apellis Pharmaceuticals, was responsible for study design and data analysis, with input from investigators and other retinal specialists. See the Appendix (available at www.aaojournal.org) for further details. The trial is registered with ClinicalTrials.gov (identifier, NCT02503332). Apellis provided the study drug.

Patients

Eligible patients were at least 50 years of age and fulfilled the following major criteria with reference to the study eye: best-corrected visual acuity (BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study charts (20/320 Snellen equivalent), diagnosis of GA secondary to AMD confirmed using fundus autofluorescence imaging with GA area size of 2.5 mm^2 or more and 17.5 mm^2 or less, presence of any pattern of hyperautofluorescence in the junctional zone of GA, and at least 1 focal lesion of 1.25 mm^2 or more if GA was multifocal. Geographic atrophy, exudative AMD, or both were permitted in the contralateral eye. An independent central reading center (Digital Angiography Reading Center, Great Neck, NY) confirmed lesion eligibility. Major exclusion criteria with reference to the study eye included GA secondary to causes other than AMD, history or current evidence of exudative AMD, and retinal disease other than AMD. For a complete list of eligibility criteria, see the Appendix.

Outcome Measures

The primary efficacy end point was the change from baseline to month 12 in the square root of the GA lesion area as assessed using fundus autofluorescence imaging. Images were assessed by the central reading center. Applying the square root transformation to GA lesion area measurements has been shown to eliminate the dependence of GA lesion growth rate on baseline area.[25–29] Secondary outcome measures included mean change from baseline to month 12 for each of the following: untransformed GA lesion area, distance of GA lesion from the fovea (foveal encroachment) measured using fundus

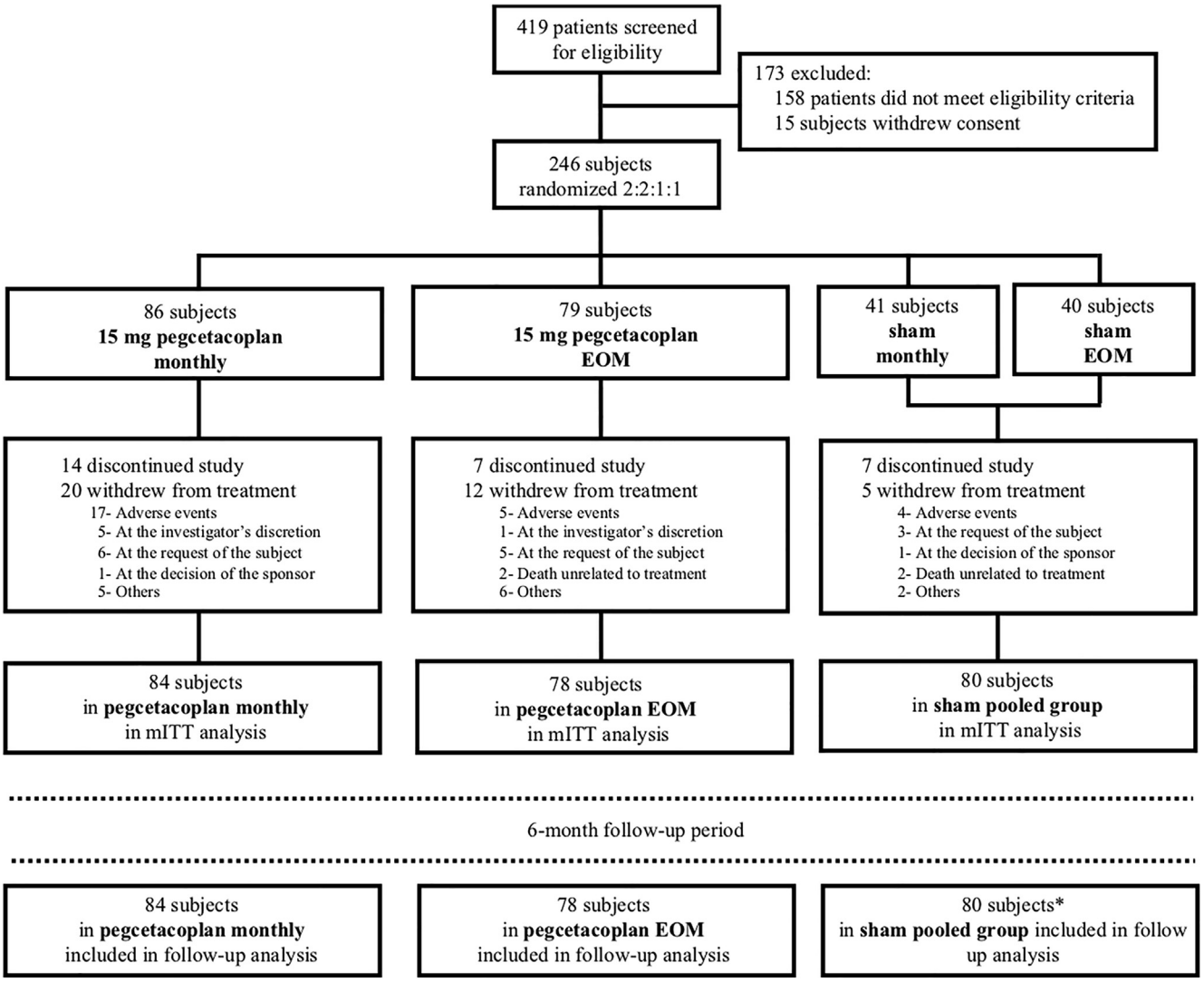

Figure 1. Clinical trial flowchart. Eligible patients were randomized to receive intravitreal sham injections or intravitreal injections of pegcetacoplan monthly or every other month (EOM) for 12 months. Patients returned at months 15 and 18 for safety and efficacy follow-up, with the exception of an additional 5, 7, and 8 patients in the sham, pegcetacoplan monthly, and pegcetacoplan EOM groups, respectively. A modified intention-to-treat (mITT) population was used for the efficacy analysis and was defined as all patients who received at least 1 injection and underwent at least 1 follow-up examination at month 2 or later at which primary efficacy data were collected. *n = 80 patients in the analysis of geography atrophy change because of missing evaluable data after baseline for 1 patient.

autofluorescence imaging, BCVA, low-luminance BCVA (LL-BCVA), and low-luminance visual acuity deficit (LL-VD). Low-luminance visual acuity deficit was derived by subtracting LL-BCVA from BCVA. The primary safety end point was the frequency and severity of treatment-emergent adverse events.

Genetic Analysis

Blood samples were collected for genetic marker analysis and genotyped on the Axiom Precision Medicine Chip (Thermo Fisher Scientific, Waltham, MA). Variants were called with the Axiom Analysis Suite using the Best Practice Workflow (see Appendix for details).

Statistical Analysis

A sample size of 240 patients (pegcetacoplan monthly, n = 80; pegcetacoplan EOM, n = 80; sham monthly, n = 40; and sham EOM, n = 40) was calculated to provide approximately 90% power to detect a 30% reduction in annual square root area increase of square root GA area for the pegcetacoplan-treated groups compared with the pooled sham group. Calculations assumed average square root GA area change of 0.33 mm/year without treatment, standard deviation of annual square root area change of 0.2 mm/year,[25,29] and a 15% to 20% loss to follow-up by month 12 and were based on 2-sided t tests at the $\alpha = 0.1$ level.

All efficacy analyses were performed on the modified intention-to-treat population, defined as all patients who received at least 1 injection and had undergone at least 1 examination at month 2 or later at which primary efficacy data were collected (Fig 1). The sham groups were pooled for all analyses. Changes from baseline in the square root GA lesion area measurements at months 2, 6, 12, and 18 were estimated with a linear mixed-effects model for repeated measures using observed data. The linear mixed-effect model included treatment and visit as factors

Table 1. Baseline Characteristics of the Intention-to-Treat Population

Parameters	Sham Pooled (n = 81)	Pegcetacoplan Monthly (n = 86)	Pegcetacoplan Every Other Month (n = 79)
Patient demographics			
Age (yrs), mean (SD)	78.4 (7.43)	79.6 (7.51)	80.9 (7.55)
Female gender, no. (%)	49 (60.5)	55 (64.0)	50 (63.3)
White race, no. (%)	81 (100.0)	84 (97.7)	76 (96.2)
Study characteristics			
Total area of GA (mm^2), mean (SD)	8.2 (4.05)	8.0 (3.85)	9.0 (4.47)
Square root area of GA (mm), mean (SD)	2.8 (0.72)	2.7 (0.67)	2.9 (0.77)
Bilateral GA, no. (%)	72 (88.9)	71 (82.6)	64 (81.0)
CNV in the fellow eye, no. (%)	29 (35.8)	36 (41.9)	28 (35.4)
BCVA letter score, mean (SD)	59.8 (17.2)	59.8 (15.7)	58.4 (16.0)
20/200 or worse	12 (14.8)	9 (10.5)	10 (12.7)
20/160–20/50	33 (40.7)	50 (58.1)	44 (55.7)
20/40 or better	36 (44.4)	27 (31.4)	25 (31.6)
Snellen equivalent (median)	20/50	20/63	20/63
LL-BCVA letter score, mean (SD)	33.6 (17.8)	36.3 (16.6)	31.4 (17.1)
Snellen equivalent (median)	20/200	20/200	20/250
LL-VD letter score, mean (SD)	26.2 (17.1)	23.5 (14.5)	27.1 (15.7)

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; GA = geographic atrophy; LL-BCVA = low-luminance best-corrected visual acuity; LL-VD = low-luminance visual acuity deficit, which is derived by subtracting LL-BCVA from BCVA; SD = standard deviation.

and baseline GA lesion as a covariate, as well as the interaction term of treatment by visit and visit by baseline. Changes in GA lesion area, foveal encroachment, BCVA, LL-BCVA, and LL-VD were estimated using the same approach. All statistical tests were 2 sided at the 0.1 level of significance. There were no adjustments for multiple comparisons. Safety data were collected for all randomized patients who received at least 1 injection and were analyzed using observed data without imputation. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Patients

Between September 24, 2015, and July 22, 2016, 246 patients were randomized, of whom 243 met the prespecified criteria for analysis (Fig 1). The pegcetacoplan and sham groups were comparable with regard to baseline demographic and ocular characteristics (Table 1) and exhibited a genotype profile typical of patients with GA secondary to AMD (Table S1, available at www.aaojournal.org). A total of 218 of 246 patients (88.6%) completed the first 12 months of the study, during which patients in the monthly pegcetacoplan and monthly sham groups received an average of 10.5 and 11.6 injections, respectively (of 13 possible), and patients in the EOM pegcetacoplan and EOM sham groups received an average of 6.2 and 6.6 injections, respectively (of 7 possible). Figure S1 (available at www.aaojournal.org) shows the percentage of patients in each group who continued treatment or remained in the study over time. The mean and median number of injections received by patients in each group over the 12-month treatment period is presented in Table S2 (available at www.aaojournal.org).

Efficacy

The study met its primary efficacy end point in both the pegcetacoplan monthly and EOM groups. The least squares mean change from baseline to month 12 in square root GA area was 0.25 mm in the pegcetacoplan monthly group, 0.28 mm in the pegcetacoplan EOM group, and 0.35 mm in the pooled sham group. Thus, patients treated with pegcetacoplan monthly had 29% smaller increases (95% confidence interval [CI], 9%–49%; $P = 0.008$) and patients treated with pegcetacoplan EOM had 20% smaller increases (95% CI, 0%–40%; $P = 0.067$) in square root GA lesion area growth compared with sham, respectively, meeting the prespecified significance level ($P < 0.1$). The primary efficacy results, including outcomes at month 18, are presented in Figure 2. The robustness of the primary efficacy results was supported by multiple sensitivity analyses (Table S3A, available at www.aaojournal.org). Pegcetacoplan led to 30% and 20% reductions in untransformed GA lesion area growth at month 12 in the monthly and EOM treatment groups, respectively,

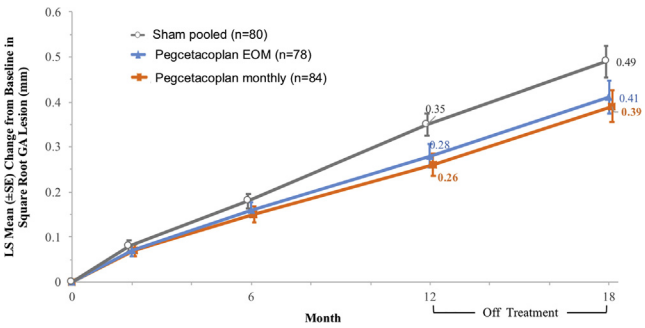

Figure 2. Graph showing the change from baseline in square root geographic atrophy (GA) area measurements in the study eye. Least squares (LS) means and their standard errors (SEs) were estimated from a mixed-effect model that included treatment and visit as factors and baseline geographic atrophy (GA) lesion as a covariate, as well as the interaction term of treatment × visit and visit × baseline. The *P* values versus the sham-pooled arm for pegcetacoplan monthly and every other month (EOM) treatment, respectively, were 0.010 and 0.061 at month 12 and 0.044 and 0.097 at month 18. There was no statistically significant difference in GA lesion growth between pegcetacoplan monthly and EOM.

consistent with the primary efficacy analysis (Fig S2, available at www.aaojournal.org).

The effect of pegcetacoplan on GA lesion growth was evident primarily between months 6 and 12. In a post hoc analysis, reductions in growth rate of square root GA lesion area of 45% (95% CI, 21−69; $P < 0.001$) and 33% (95% CI, 9−58; $P = 0.009$) compared with sham were observed in the pegcetacoplan monthly and pegcetacoplan EOM groups, respectively, during months 6 to 12 (Fig 3). Similar reductions in growth rate of untransformed GA lesion area during the second 6 months were observed (Fig S2).

The influence of 47 prespecified genetic variants associated with AMD risk, including variants in *CFH*, *CFI*, *C2/CFB*, and *C3*,[12,13] on GA growth rate and response to pegcetacoplan was investigated. None of them significantly influenced treatment effect of pegcetacoplan, indicating that pegcetacoplan's ability to slow GA lesion growth is independent of these factors (Table S4, available at www.aaojournal.org). Two genetic factors, rs2230199 in *C3* and rs3750846 in *ARMS2*, both previously shown to influence GA growth, correlated with GA growth rate in this study independently of treatment assignment (Table S5, available at www.aaojournal.org).[30]

The effect of pegcetacoplan on GA lesion growth declined on cessation of treatment, confirming that the reduced growth rate during treatment was attributable to pegcetacoplan. The observed mean changes from months 12 to 18 in the 3 groups were comparable (Fig 3). Pegcetacoplan had no effect on changes in foveal encroachment, visual acuity measures, or LL-VD at month 12 compared with sham treatment. All groups exhibited a gradual decline in visual acuity measures and LL-VD, with no significant difference between groups (Fig 4A−C).

Safety

Adverse events are summarized in Table 2. Injection-related culture-positive endophthalmitis occurred in 2 pegcetacoplan-treated eyes. Both patients withdrew from the study. Culture-negative endophthalmitis occurred in 1 pegcetacoplan-treated eye. The patient resumed pegcetacoplan treatment after missing 1 dose.

There was a higher incidence of adverse events reported as choroidal neovascularization (CNV) or neovascular AMD in study eyes treated with pegcetacoplan (18/86 eyes [20.9%; 95% CI, 12.9−31.0] and 7/79 eyes [8.9%; 95% CI, 3.6−17.4] in the monthly and EOM groups, respectively) than in sham-treated eyes (1/81 eyes [1.2%]; 95% CI, 0−6.7), as shown in Table 2. Fluorescein angiography (FA) was performed at the discretion of the investigator in a subset of the eyes in which this event occurred. In the monthly group, FA imaging was acquired in 10 eyes and evidence of CNV was confirmed in 5 of these eyes. In the EOM group, FA was acquired in 7 eyes and CNV was confirmed in 5 of these eyes. Fluorescein angiography was not acquired in the patients in the sham group. All 10 cases of CNV confirmed by FA were classified as occult CNV by the reading center. Because the presence of CNV was not confirmed by either FA or OCT angiography in most cases, these events are referred to herein as exudative AMD. Exudative AMD was identified more frequently with monthly pegcetacoplan dosing and was more common in patients with a history of CNV in the contralateral eye (Table 2). Development of exudative AMD was not associated with any substantial change in visual acuity (Table S6, available at www.aaojournal.org). Patients who demonstrated exudative AMD showed no change in mean BCVA at the time of diagnosis compared with the visit before diagnosis. Mean BCVA at month 18 in these patients was 54 letters and was similar to that of patients who did not demonstrate this event (53 letters). There was no discernible temporal clustering of onset of exudative AMD, although most (20/26) instances were observed during the treatment period. Reading center assessment of OCT imaging performed at the time of the investigator-determined onset of exudative AMD revealed the following: 14 of 26 eyes showed subretinal fluid,

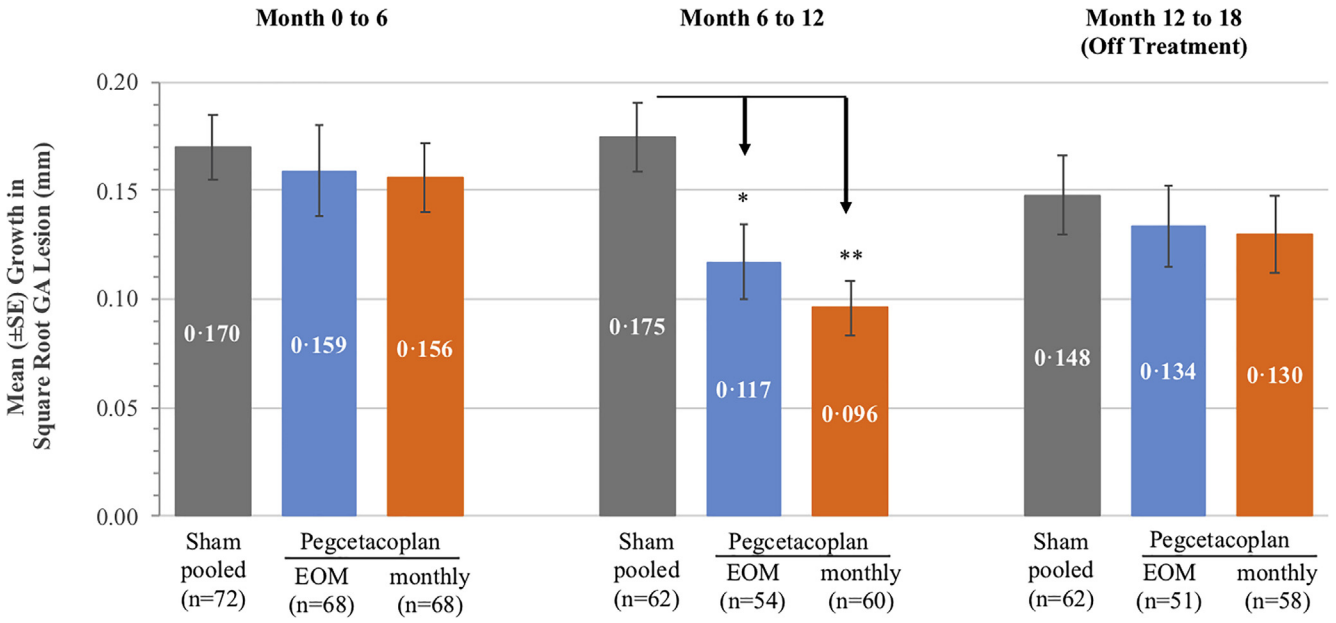

Figure 3. Bar graph showing post hoc exploratory analyses: growth in geographic atrophy (GA) lesion size (in millimeters) in the study eye per 6-month period. Means and standard errors (SEs) of patients who had values at both visits in each summary period are shown. Pairwise comparisons for either the pegcetacoplan arm versus the sham-pooled arm based on a 1-way analysis of variance using the least significant difference method for multiplicity showed no significant difference for months 0 to 6 and months 12 to 18 and showed a *P value of 0.0004 for pegcetacoplan monthly and a **P value of 0.009 for pegcetacoplan every other month (EOM) for the lesion growth from months 6 to 12.

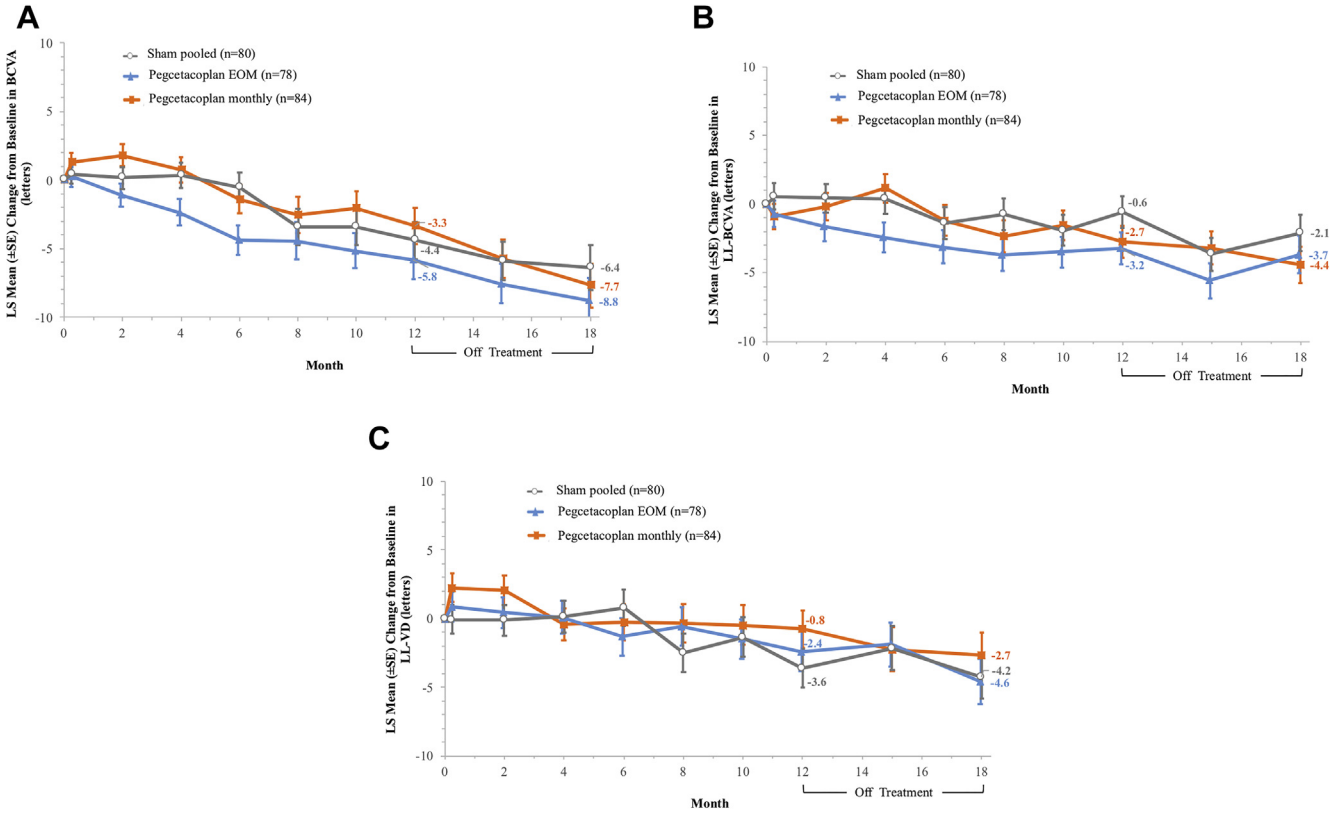

Figure 4. Graphs showing the change from baseline in visual acuity. **A**, Best-corrected visual acuity (BCVA) assessed with the Early Treatment Diabetic Retinopathy Study chart. **B**, Low-luminance BCVA (LL-BCVA). **C**, Low-luminance visual acuity deficit (LL-VD), which is derived by subtracting LL-BCVA from BCVA. Least-squares (LS) means and standard errors (SEs) were estimated from a mixed-effect model that included treatment and visit as factors and baseline value of the end point as a covariate, as well as the interaction term of treatment × visit and baseline × visit. EOM = every other month.

subretinal hyperreflective material, or both along with intraretinal cystic changes; 5 of 26 eyes showed cystic changes only; and 7 of 26 patients showed no exudative changes on OCT.

Patients who demonstrated study eye exudative AMD during the treatment period discontinued study treatment. All but 2 patients demonstrating exudative AMD were treated with VEGF inhibitors. Nineteen of the 26 patients remained in the study through month 18, and available data from these patients were included in the efficacy and safety analyses. We repeated the primary analysis excluding data from patients who demonstrated study eye exudative AMD to evaluate the impact of these data on the results. The results were consistent with those observed in the modified intention-to-treat population (Table S3B, available at www.aaojournal.org). Of note, during the 12-month treatment period, only 3 patients in the monthly pegcetacoplan-treated group and no patients in the other groups demonstrated exudative AMD in the contralateral eye. There were no reports of new-onset exudative AMD in the contralateral eye during the follow-up period.

Pegcetacoplan administration had no long-term effect on intraocular pressure, as assessed by preinjection measurements. Postinjection intraocular pressure was assessed within 15 minutes of pegcetacoplan injection, and elevations of more than 30 mmHg resolved spontaneously or with standard intraocular pressure-lowering procedures that included, but were not limited to, ocular massage, intraocular pressure-reducing medications, anterior paracentesis, or a combination thereof before patients returned home.

The incidences of treatment-emergent adverse events (TEAEs) in the study eye and of nonocular TEAEs are summarized in Table S7A and B (available at www.aaojournal.org). Nonocular TEAEs generally were typical of the elderly study population, and their incidences were similar between the pegcetacoplan and sham groups. There were 8 deaths (2 in the pegcetacoplan monthly group, 2 in the pegcetacoplan EOM group, and 4 in the sham group). No nonocular TEAEs or deaths were considered related to pegcetacoplan treatment. Hematologic analysis, urinalysis, clinical chemistry tests, and serum complement profile assays (CH50, C3 level) did not identify any patterns related to pegcetacoplan.

Discussion

The Filly study of pegcetacoplan as a therapy for GA secondary to AMD met its primary end point by reducing GA lesion growth rate by 29% and 20% compared with sham treatment in patients receiving pegcetacoplan monthly or EOM, respectively, over 12 months. The effect was particularly notable during the second 6 months of treatment, with observed reductions of 45% and 33% for pegcetacoplan monthly and EOM, respectively. The growth rate of GA lesions in the sham group was consistent with that observed in other studies of GA.[22] The ability of pegcetacoplan to reduce GA lesion growth rate markedly also was evident

Table 2. Major Safety Data in the Intention-to-Treat Population

Parameters	Sham Pooled (n = 81)	Pegcetacoplan Monthly (n = 86)	Pegcetacoplan Every Other Month (n = 79)
Adverse events, no. of patients (%)			
SAEs in the study eye	1 (1.2)	4 (4.7)	2 (2.5)
SAEs in the contralateral eye	1 (1.2)*	0	0
Systemic (nonocular) SAEs	23 (28.4)	19 (22.1)	24 (30.4)
TEAEs in the study eye	47 (58.0)	65 (75.6)	49 (62.0)
TEAEs in the contralateral eye	36 (44.4)	31 (36.0)	18 (22.8)
Systemic (nonocular) TEAEs	64 (79.0)	69 (80.2)	58 (73.4)
Treatment-related AEs in the study eye	0	22 (25.6)	11 (13.9)
Systemic (nonocular) treatment related AEs	0	0	0
Ocular SAEs in the study eye, no. of patients (%), no. of events			
Endophthalmitis†	0	2 (2.3), 2	1 (1.3), 1
Intraocular pressure increased	0	1 (1.2), 2	1 (1.3), 1
Retinal detachment	0	1 (1.2), 1	0
Dry AMD	1 (1.2), 1	0	0
Incidence of exudation in the study eye during study (as determined by the investigator)			
Patients with exudation in the study eye (%)	1 (1.2)	18 (20.9)	7 (8.9)
95% exact CI for incidence	0.0%–6.7%	12.9%–31.0%	3.6%–17.4%
With history of CNV in contralateral eye, no. of patients	29	36	28
Patients with exudation in the study eye (%)	0	12 (33.3)	5 (17.9)
95% exact CI for incidence	0.0%–11.9%	18.6%–51.0%	6.1%–36.9%
No CNV history in contralateral eye, no. of patients	52	50	51
Patients with exudation in the study eye (%)	1 (1.9)	6 (12.0)‡	2 (3.9)
95% exact CI for incidence	0.0%–10.3%	4.5%–24.3%	0.5%–13.5%

AE = adverse event; AMD = age-related macular degeneration; CI = confidence interval; CNV = choroidal neovascularization; SAE = serious adverse event; TEAE = treatment emergent adverse event.
*Case of facial bone fracture.
†Two culture-positive results for coagulase-negative *Staphylococcus*.
‡One culture-negative result in the monthly group.

in comparisons of pegcetacoplan-treated eyes versus contralateral eyes in patients with bilateral GA and followed a similar time course. Treatment benefit from pegcetacoplan was independent of genetic risk factors historically associated with AMD tested in the study. The treatment effect was maintained over the 18-month study. However, GA growth rate in pegcetacoplan-treated eyes began increasing after cessation of treatment at 12 months, suggesting a need for continuous therapy.

The safety profile was similar to that observed in studies of other intravitreally administered drugs[22,31–33] with the exception of the development of exudative AMD. Two cases of culture-positive endophthalmitis, a known potential complication of intravitreal injections, occurred in eyes treated with pegcetacoplan. This risk may be mitigated in the future through the use of a liquid pegcetacoplan formulation that does not require reconstitution. Rates of nonocular TEAEs in the pegcetacoplan-treated and sham groups did not differ significantly, and none was attributed to pegcetacoplan. A higher incidence of exudative AMD was observed in eyes treated with pegcetacoplan compared with sham treatment, occurring primarily in patients with a history of contralateral eye CNV, and was managed with anti-VEGF drugs. The historical incidence of contralateral-eye CNV in patients with unilateral exudative AMD ranges from 6% to 12% per year in various studies, similar to the incidence of exudative AMD among patients with contralateral-eye CNV who received pegcetacoplan EOM.[34,35] However, the difference in incidence of new-onset exudative AMD between pegcetacoplan-treated eyes and sham-treated eyes, with the appearance of a dose response, suggests that pegcetacoplan altered the course of AMD.

Complement activation via all 3 activation pathways leads to cleavage of complement C3 into C3a and C3b, followed by convertase formation, C5 activation, and formation of the membrane attack complex. A number of compounds that target various components of the complement system have been tested in clinical trials in GA. Inhibition downstream of C3 at the level of C5, or inhibition of factor D, a key alternative pathway component, failed to reduce GA lesion growth compared with sham treatment,[22,25] raising the question of why C3 inhibition would be effective when other strategies targeting complement were not. We hypothesize that one mechanism by which complement activation is pathogenic in GA is related to an imbalance in deposition and removal of C3 fragments on the retinal pigment epithelium, photoreceptors, capillary endothelial cell surfaces, or a combination thereof, resulting in C3 fragment accumulation, which promotes phagocytosis by microglia or macrophages. Observations in other pathologic settings support this hypothesis. The accumulation of C3b and its fragments (iC3b, C3dg, C3d) on mammalian cell surface has been demonstrated to promote phagocytosis

by macrophages and microglia.[36–38] In addition, activated macrophages and microglia are associated with retinal degeneration in several experimental and clinical conditions, including AMD.[23,39–41] We hypothesize that oxidative stress-mediated reduction in endocytosis may contribute to the accumulation of C3 fragments at the surface of cells affected in GA. Consistent with this hypothesis, in vitro studies have demonstrated that retinal pigment epithelium cells can use endocytosis as a strategy to prevent accumulation of complement components at the cell surface.[42] By inhibiting C3 activation, pegcetacoplan would prevent further C3 deposition, allowing cells to avoid phagocytosis and to survive. In the absence of ongoing phagocytic attack, viable endothelium in the choriocapillaris adjacent to areas of GA may regrow new vessels. Because these vessels would lack the barrier functions of mature endothelium, they may have increased propensity to leak, which may explain the higher incidence of exudative AMD observed in pegcetacoplan-treated eyes relative to sham.

C3 inhibition may have additional effects on the activity of microglia and macrophages. These cells have been classified broadly into 3 categories: (1) resting M0; (2) proinflammatory, prophagocytic M1; and (3) reparative, proangiogenic M2 phenotypes, but exhibit high phenotypic plasticity in response to changes in their local microenvironment.[43,44] An analysis of macrophage polarization in postmortem eyes of patients with or without AMD showed that there is a tendency toward greater M1 activity in GA and more M2 activity in exudative AMD.[39] Several lines of evidence suggest that the C5 activation product C5a can polarize macrophages toward an M1 phenotype and that lack of complement results in a shift toward M2.[45,46] We hypothesize that complement inhibition with pegcetacoplan, by blocking the activation of C3 and preventing formation of downstream effectors such as C5a, may permit M1 macrophages and microglia to transition to a proangiogenic, reparative M2 phenotype in the setting of GA, before reverting to a resting M0 stage.[44]

This study had limitations. The functional outcomes assessed measure central vision, which can remain relatively well preserved for a time in patients with GA, despite functional loss in extrafoveal regions of the retina and progression of atrophy that ultimately will lead to severe central vision deficits. Measures of central vision do not reflect the full spectrum of impairments experienced by patients with GA, and this limited the ability to detect functional benefit. Alternative functional assessments such as reading speed and evaluation of retinal function by microperimetry may be better indicators of retinal function and health. Another limitation was that patients who demonstrated study eye exudative AMD discontinued treatment, so it was not possible to investigate the ability of ongoing pegcetacoplan therapy to reduce GA lesion growth further in this population. These limitations will be addressed in phase 3 studies, in which additional functional outcome measures will be assessed and patients who demonstrate exudative AMD will continue study treatment in addition to receiving VEGF inhibitor therapy.

In conclusion, this is the first study that demonstrated that C3 inhibition can slow the progression of GA. Treatment with pegcetacoplan was associated with significant reductions in GA lesion growth during 12 months of therapy, particularly during the latter 6 months, and demonstrated acceptable safety to proceed to phase 3 studies. These studies will define the efficacy and safety profile of pegcetacoplan further as a treatment for patients with GA, a blinding disease with no approved therapies.

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Footnotes and Financial Disclosures

Originally received: February 2, 2019.
Final revision: June 27, 2019.
Accepted: July 9, 2019.
Available online: July 16, 2019. Manuscript no. 2018-2674.

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Presented at: American Academy of Ophthalmology Annual Meeting, New Orleans, Louisiana, November 2017; American Academy of Ophthalmology Annual Meeting, Chicago, Illinois, October 2018; Association for Research in Vision and Ophthalmology Annual Meeting, Honolulu, Hawaii, April 2018; and Annual Macula Society Meeting, Beverly Hills, California, February 2018.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): D.S.L.: Financial support − Apellis.

F.V.G.: Employee and Equity owner − Apellis; Patent − 15/766,795.

D.E.M.: Employee and Equity owner − Apellis.

M.R.G.: Employee and Equity owner − Apellis.

D.M.B.: Financial support − Adverum Bio, Allergan, Apellis, Chengdu Kanghong, Clearside, Genentech/Roche, Heidelberg, Novartis, OHR, Regeneron, Regenxbio, Samsung, Tyrogenex, Aerpio, Allegro, Ophthea, Biotime, Optos, Senju, Stealth Bio.

J.S.H.: Financial support − Aerpio, Apellis, Corcept, Daiichi Sankyo, Genentech, Genzyme, Hemera, Janssen R&D, Kalvista, Ocudyne, Ophthotech, Optovue, Regeneron, Regenxbio, Scifluor, Tyrogenex, 4DMT, Adverum, Aerie, Aerpio, Allegro, Apellis, Array, Asclepix, Bayer, BeaverVisitec, BioMarin, Clearside, Corcept, Daiichi Sankyo, Galecto, Genentech/Roche, Helio, Hemera, Interface, iRenix, Kanghong, Kodiak, Notal Vision, Novartis, Ocular Therapeutix, Optos, Orbit Biomedical, Quark, Ra Pharmaceuticals, Regeneron, Regenxbio, Santen, Scifluor, Shire, Spark Therapeutics, Stealth, Thrombogenics, Tyrogenex.

C.C.W.: Consultant − Alimera Sciences, Alnylam, Avalere, Bayer, Clearside, EyePoint (formerly pSivida), Genentech, Notal Vision, Novartis, ONL Therapeutics, PolyPhotonix, RecensMedical, Regeneron, Roche, Santen, D.O.R.C.; Financial support − Acucela, Adverum, Aerpio, Alcon, Aldeyra, Astellas, Aura, Boehringer Ingelheim, Chiltern, Heidelberg Engineering, Iconic, OHR, ONL Therapeutics, Ophthotech, Opthea, Regenxbio, SciFluor, Taiwan Liposome Company, ThromboGenics, Tyrogenex, Alimera Sciences, Alnylam, Avalere, Bayer, D.O.R.C., Notal Vision, ONL Therapeutics, PolyPhotonix, RecensMedical, Allegro, Allergan, Apellis, Clearside, EyePoint (formerly pSivida), Genentech, Novartis, Regeneron, Roche, Santen.

L.J.S.: Financial support − Apellis, Genentech, Novartis, Ophthotech, Roche.

P.A.: Financial support − Apellis.

B.H.F.W.: Financial and nonfinancial support − Allergan Limited (United Kingdom), Alcon, Apellis, Novartis.

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J.S.S.: Financial support − Apellis, GSK, Johnson & Johnson, Gilead, Opthea, Sanofi, Samsung, Mylan, Roche; Equity owner − Apellis.

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Support by Apellis Pharmaceuticals.

HUMAN SUBJECTS: Human subjects were included in this study. Institutional Review Board Approval was obtained from each of the 46 sites in the United States (New England Institutional Review Board, University of Miami, Mayo Clinic, Institutional Review Board of the Cleveland Clinic Foundation, Duke University Health System Institutional Review Board, and Research Compliance Office, Stanford University), Australia (Bellberry Ltd), and New Zealand (Northern A Health and Disability Ethics Committee, Health and Disability Ethics Committees, and Ministry of Health). The study was performed in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and all applicable regulations. All subjects provided written informed consent.

No animal subjects were included in this study.

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Obtained funding: N/A

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CNV** = choroidal neovascularization; **EOM** = every-other-month; **FA** = fluorescein angiography; **GA** = geographic atrophy; **LL-BCVA** = low-luminance best-corrected visual acuity; **LL-VD** = low-luminance visual acuity deficit; **SE** = standard error; **TEAE** = treatment emergent adverse event; **VEGF** = vascular endothelial growth factor.

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