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Characterizing New-Onset Exudation in the Randomized Phase 2 FILLY Trial of Complement Inhibitor Pegcetacoplan for Geographic Atrophy

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Objectives: To evaluate clinical characteristics of eyes in which investigator-determined new-onset exudative age-related macular degeneration (eAMD) developed during the FILLY trial.

Design: Post hoc analysis of the phase 2 study of intravitreal pegcetacoplan in geographic atrophy (GA).

Subjects: Patients with GA secondary to age-related macular degeneration (AMD), n = 246.

Intervention: Either 15 mg intravitreal pegcetacoplan or sham given monthly or every other month for 12 months followed by a 6-month off-treatment period.

Main Outcome Measures: Time of new eAMD onset in the study eye, history of eAMD in the fellow eye, presence of double-layer sign (DLS) on structural OCT in the study eye, changes in retinal anatomic features by structural OCT and fluorescein angiography (FA), and changes in visual acuity.

Results: Exudation was reported in 26 study eyes across treatment groups over 18 months. Mean time to eAMD diagnosis was 256 days (range, 31−555 days). Overall, a higher proportion of patients with a baseline history of eAMD in the fellow eye ($P = 0.016$) and a DLS in the study eye ($P = 0.0001$) demonstrated eAMD. Among study eyes in which eAMD developed, 18 of 26 (69%) had history of fellow-eye eAMD and 19 of 26 (73.1%) had DLS at baseline, compared with 76 of 217 study eyes (35%; $P = 0.0007$) and 70 of 215 study eyes (32.5%; $P < 0.0001$), respectively, in which eAMD did not develop. All 21 patients with structural OCT imaging at the time of eAMD diagnosis demonstrated subretinal fluid, intraretinal cysts, or both consistent with exudation. Among 17 patients who underwent FA at eAMD diagnosis, 10 showed detectable macular neovascularization (MNV), all occult lesions. Development of eAMD did not have an appreciable impact on visual acuity, and all patients responded to anti−vascular endothelial growth factor (VEGF) therapy.

Conclusions: Intravitreal pegcetacoplan slowed the rate of GA growth and was associated with an unexpected dose-dependent increased incidence of eAMD with no temporal clustering of onset. Exudative AMD seemed to be associated with baseline eAMD in the contralateral eye and a DLS, suggestive of nonexudative MNV, in the study eye. The safety profile of pegcetacoplan was acceptable to proceed to phase 3 studies without adjustments to enrollment criteria. *Ophthalmology 2021;■:1−12 © 2021 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/).*

Age-related macular degeneration (AMD) is a late-onset complex genetic disorder, the pathophysiologic characteristics of which involve potential disease-causing variants in complement genes,[1−3] and is the leading cause of irreversible vision loss among the elderly worldwide.[4] Age-related macular degeneration can be divided into 3 main clinical stages (early, intermediate, and late) based on overall disease severity,[5] with decreased quality of life and significant visual impairment occurring during the late stage. Late AMD can be subdivided into the exudative form, which is characterized by the presence of macular neovascularization (MNV), and the nonexudative form, known as geographic atrophy (GA), which is characterized by progressive loss of macular photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris.[6,7] Geographic atrophy is also referred to as complete RPE and outer retinal atrophy.[8] Importantly, MNV and exudation refer to 2 distinct entities, because neovascular AMD can be classified into a number of subtypes, including nonexudative and exudative forms.[9] The exudative form of AMD (eAMD) can be treated with intravitreal injections of vascular endothelial growth factor (VEGF) A inhibitors.[10] Although anti-VEGF therapy has been shown to improve vision and reduce the risk of severe

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vision loss over several years in eyes with eAMD,[11–13] the nonexudative form of AMD can continue to progress to macular atrophy, apparently independent of the exudative process.[14] For most patients with late AMD, macular atrophy is the characteristic end stage of the disease process, resulting in progressive and irreversible loss of visual function as the area of macular atrophy enlarges.[15]

Currently, no approved therapies exist to prevent or slow the progression of GA and inhibit associated vision loss. Recently, the phase 2 FILLY trial (NCT02503332) evaluating 15 mg of intravitreal pegcetacoplan, an inhibitor of complement C3 cleavage, demonstrated a statistically significant reduction in the enlargement rate of GA lesions after treatment monthly or every other month (EOM; 29% and 20% reductions, respectively) compared with sham treatment.[16] These phase 2 results led to 2 ongoing confirmatory phase 3 trials (DERBY [ClinicalTrials.gov identifier, NCT03525600] and OAKS [ClinicalTrials.gov identifier, NCT03525613]) designed to evaluate the efficacy and safety of intravitreal pegcetacoplan for the treatment of GA in AMD.

In the FILLY trial, a higher incidence of investigator-determined new-onset eAMD occurred in eyes treated with pegcetacoplan compared with eyes receiving sham treatment.[16] Over the 18-month course of the study, including a 6-month off-drug follow-up period, eAMD was diagnosed in 18 of 86 eyes (20.9%) receiving monthly pegcetacoplan, 7 of 79 eyes (8.9%) receiving EOM pegcetacoplan, and 1 of 81 eyes (1.2%) receiving sham injections. At month 12, the end of the active treatment period of the trial, eAMD was observed in 14 of 86 eyes (16.3%) in the monthly arm, 5 of 79 eyes (6.3%) in the EOM arm, and 1 of 81 eyes (1.2%) in the sham arm. The current post hoc analysis was conducted to analyze the risk factors, clinical characteristics, and clinical outcomes of study eyes with new-onset, investigator-determined eAMD during the FILLY trial.

Methods

Study Design

The FILLY study was a phase 2, prospective, randomized, multicenter, single-masked, sham injection-controlled study to assess the safety, tolerability, and efficacy of intravitreally administered pegcetacoplan in patients with GA secondary to AMD. The detailed study design has been published,[16] and the trial is registered with ClinicalTrials.gov (identifier, NCT02503332). In brief, a total of 246 participants were randomized in a 2:2:1:1 ratio to receive 15 mg intravitreal pegcetacoplan monthly, 15 mg intravitreal pegcetacoplan EOM, sham injection monthly, or sham injection EOM for 12 months. After the 12-month primary end point, all patients were followed up for an additional 6 months off-treatment. The patients, photographers, and visual acuity examiners were masked to the specific treatment being administered, and masking was maintained through month 18. The investigators, study site personnel not performing assessments of efficacy variables, vendors, and sponsor personnel were unmasked to treatment assignment.

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 approval for the phase 2 FILLY study was obtained at each clinical site. All participants provided written informed consent.

Eligible patients were aged 50 years or older with study eye best-corrected visual acuity (BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study charts (Snellen equivalent, approximately 20/320), diagnosis of GA secondary to AMD confirmed using fundus autofluorescence imaging with total GA area size of 2.5 to 17.5 mm^2, presence of any pattern of autofluorescence in the junctional zone of GA, and if GA was multifocal, then at least 1 focal lesion measuring at least 1.25 mm^2. Exclusion criteria included GA secondary to causes other than AMD, history or current evidence of eAMD in the study eye, and retinal diseases other than AMD. Current or prior eAMD in the contralateral, nonstudy eye was permitted.

An independent, masked central reading center (CRC; Digital Angiography Reading Center) confirmed lesion eligibility and assessed all images throughout the duration of the study. Two independent masked readers assessed the images and a third masked reader served as an adjudicator in case of disagreement between the first 2 readers.

Management of New-Onset Exudative Age-Related Macular Degeneration during the FILLY Study

No protocol-specified plan was in place for the diagnosis or management of new-onset eAMD in the study eye. This was managed according to investigator discretion, which could have included imaging with structural OCT, fluorescein angiography (FA), or both to determine or confirm the development of eAMD, as well as initiation, choice, and dosing regimen of anti-VEGF therapy. Dosing of pegcetacoplan was discontinued after the diagnosis of eAMD, but investigators were encouraged to maintain the patients in the study and to continue to monitor them at regularly scheduled visits per the protocol.

Outcomes

Main outcomes presented in the current report include time of onset of investigator-determined new-onset eAMD in the study eye, history of eAMD in the fellow eye, the presence of the double-layer sign (DLS) in the study eye, changes in retinal anatomic features assessed by structural OCT and FA, and changes in Early Treatment Diabetic Retinopathy Study letter visual acuity.

The DLS on structural OCT was defined as the presence of an irregular low-lying RPE detachment with low internal reflectivity of more than 250 μm in greatest horizontal linear dimension (Fig 1).[17,18] Three independent graders (P.J.R., the Digital Angiography Reading Center, and N.K.W.) masked to treatment assignment evaluated all baseline structural OCT images of study eyes to evaluate for the presence of a DLS. N.K.W. adjudicated when there was disagreement between P.J.R. and the Digital Angiography Reading Center to reach a consensus grading for each patient.

The presence of exudation was determined using macular structural OCT imaging to assess changes in central retinal thickness (CRT); the presence of intraretinal cysts, defined as cystoid spaces anywhere within the volume scan; and subretinal fluid (SRF) anywhere within the volume scan. When available, FA imaging was graded for the presence and type of MNV. All parameters were assessed in temporal relationship to a diagnosis of eAMD using 4 visit definitions: (1) the baseline visit, (2) the visit before the diagnosis of eAMD (closest preceding protocol-specified visit), (3) the visit at eAMD diagnosis, and (4) the final (last) visit or month 18 visit, whichever occurred later. All imaging

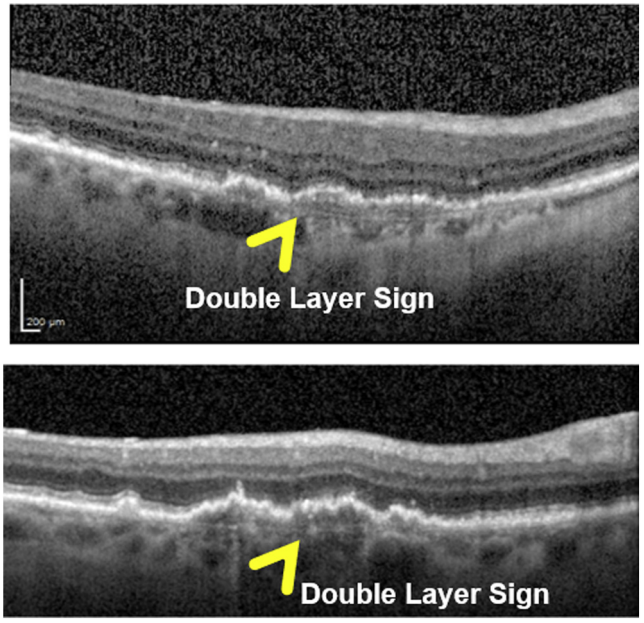


Figure 1. OCT B-scans obtained at baseline from study eyes showing a shallow irregular elevation of the retinal pigment epithelium (RPE) referred to as a double-layer sign (arrow), which is a separation between the RPE and Bruch's membrane that likely corresponds to a treatment-naïve, nonexudative type 1 macular neovascular lesion.

methods presented here were assessed by the CRC during the study with readers being unaware of which images belonged to patients with eAMD.

Statistical Methods

All patients with new-onset eAMD were documented and observed throughout the study during both the on-drug period from 0 to 12 months and the off-drug follow-up period from 13 to 18 months. New-onset eAMD rates by fellow-eye eAMD status at baseline and study-eye DLS status at baseline were compared using chi-square and Fisher exact tests. Both baseline fellow-eye eAMD status and study-eye DLS status by treatment group were compared using chi-square tests. All tests were performed at the 0.05 level without any adjustment for multiplicity. Other analyses (structural OCT, FA, BCVA) were qualitative because of limited numbers and grouping of patients with new-onset eAMD.

Results

This report represents a post hoc analysis of the risk factors, clinical characteristics, and clinical outcomes of eyes with new-onset investigator-determined eAMD during the FILLY trial.

Time of Onset of Exudative Age-Related Macular Degeneration and Anti–Vascular Endothelial Growth Factor Pharmacotherapy

Investigator-determined exudation was reported in 26 of 246 patients (10.6%) across all 3 treatment groups. Mean time to diagnosis of eAMD was 256 days (8.53 months; range, 31–555 days or 1.0–18.5 months). No apparent temporal clustering of the eAMD diagnosis was found during any timeframe through month 18, which included the on-drug and off-drug periods (Fig 2). On diagnosis of new-onset eAMD, study drug treatment was discontinued in all patients. These patients were followed up after the discontinuation of the study drug for a mean duration of 6.9 ± 5.5 months (range, 0–15.9 months) with 13 of 26 patients (50%) being followed up for 5 months or more through month 18. Overall, 92% of patients (24/26) with new-onset eAMD in the study eye received anti-VEGF therapy with a mean of 4.95 intravitreal anti-VEGF injections per patient (range, 1–14 injections), or an average of 0.7 ± 0.4 injections per month per patient, for the remaining time within the study. Two patients were not treated with anti-VEGF therapy during the study; 1 patient was diagnosed with eAMD at the final month 18 visit and another patient was diagnosed with eAMD at day 270, corresponding to month 9. In addition to these 26 investigator-determined patients with eAMD, six patients with new-onset exudation were identified retrospectively by the CRC from the per-protocol FA images obtained at the final month 18 visit. Among these patients whose disease was neither clinically

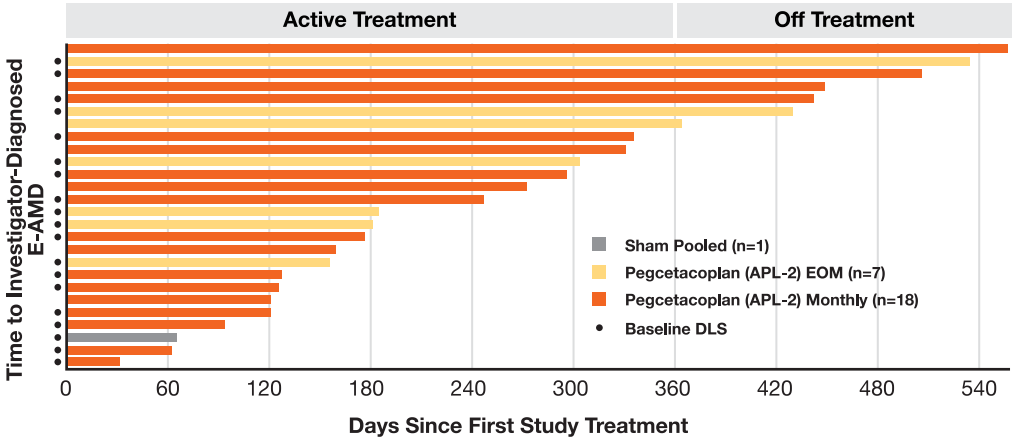


Figure 2. Bar graph showing time of onset of investigator-determined exudative age-related macular degeneration (eAMD) in the study eye through the duration of FILLY study. The duration of follow-up for patients before eAMD developing within the pegcetacoplan monthly arm (n = 18), the pegcetacoplan every other month (EOM) arm (n = 7), or the sham arm (n = 1) are depicted by the length of the horizontal bars. Pegcetacoplan dosing and sham injections were discontinued after the diagnosis of investigator-determined eAMD. The presence of baseline double-layer signs (DLSs) at baseline are indicated.

confirmed nor diagnosed by investigators, all were classified as having occult MNV; 2 patients were in the monthly arm, 3 patients were in the EOM arm, and 1 patient was in the sham arm. These patients were not included in the current analyses because they were not diagnosed by the investigators.

Ocular History of Exudative Age-Related Macular Degeneration in the Fellow Eye and Association with New-Onset Exudative Age-Related Macular Degeneration in the Study Eye

Among patients enrolled in FILLY, data related to eAMD history in the fellow eye was available for 243 patients, and 90 patients (37%) had a history of eAMD in the fellow eye, constituting 41.9%, 35.4%, and 35.8% of eyes in the monthly, EOM, and sham arms, respectively.[16] Among the 26 patients who demonstrated eAMD in the study eye, 18 (69%) had a history of eAMD in the fellow eye. In contrast, among the 217 patients who did not demonstrate eAMD in the study eye, 76 (35%) had a history of eAMD in the fellow eye ($P = 0.0007$). Table 1 depicts eAMD rates in the study eye based on fellow-eye eAMD status by treatment group. Fellow-eye eAMD status at baseline was associated with an increased rate of eAMD development in the pegcetacoplan monthly arm by month 18 ($P = 0.016$).

Double-Layer Sign and Association with New-Onset Exudative Age-Related Macular Degeneration in the Study Eye

Among patients enrolled in FILLY, DLS data at baseline in the study eye were available for 241 patients, and 89 patients (36.9%) had a consensus diagnosis of a DLS. Independent graders were in complete agreement for 77% of images; for the remaining 23% of images, adjudication was approximately even between the graders. When considered by treatment groups, the monthly treatment arm had a relatively higher proportion (40/85 [47.1%]) of eyes with DLS at baseline compared with the EOM arm (25/75 [33.3%]; $P = 0.0777$) and the sham arm (24/81 [29.6%]; $P = 0.0211$). Overall, a higher proportion of eyes with a DLS demonstrated eAMD; specifically, among patients who demonstrated eAMD in the study eye, 19 of 26 patients (73.1%) showed a DLS at baseline, and among patients who did not demonstrate eAMD in the study eye, 70 of 215 patients (32.5%) showed a DLS at baseline ($P < 0.0001$). When considered by treatment groups, this was statistically significant only within the EOM group ($P = 0.005$; Table 2). No apparent temporal correlation between the presence of DLS at baseline and the onset of exudation was observed; however, patient numbers were insufficient to confirm this observation definitively.

Retinal Anatomic Changes and New-Onset Exudative Age-Related Macular Degeneration in the Study Eye

Figure 3 shows the proportion of patients with cystoid spaces and SRF, as well as CRT from available data at the defined time points. At baseline, among patients who demonstrated eAMD in the study eye, 5 of 26 patients (19%) and 2 of 26 patients (8%) showed cystoid spaces and SRF, respectively, and mean CRT was 145 μm; and at the visit before eAMD diagnosis, 11 of 26 patients (42%) and 5 of 26 patients (19%) showed cystoid spaces and SRF, respectively. By comparison, among the 217 patients who did not demonstrate eAMD in the study eye, at baseline 38 of 217 patients (18%) and 11 of 217 patients (5%) showed cystoid spaces and SRF, respectively, and mean CRT was 125 μm; at the time of eAMD diagnosis, 16 of 21 patients (76%) and 13 of 21 patients (62%) showed cystoid spaces and SRF, respectively. At month 18, the corresponding percentages decreased to 6% (1/17) and 12% (2/17), respectively (Fig 3A) among patients who demonstrated eAMD. For the rest of the cohort (n = 176), the percentage of patients at month 18 with cystoid spaces and SRF was 13% (22/176) and 3% (6/176), respectively.

At the time of eAMD diagnosis, the average increase in CRT was 60 μm (n = 21) compared with baseline (n = 26; Fig 3B; when 21 patients with available data at both of these time points were compared, CRT increase was 68 μm [data not shown]). From the visit before the diagnosis of eAMD (n = 26) to the time of eAMD diagnosis (n = 21), the average increase in CRT was 54 μm (Fig 3B; when 21 patients with available data at both these time points were compared, CRT increase was 66 μm [data not shown]). At month 18, CRT returned to baseline (n = 17; Fig 3B; CRT for these 17 patients at baseline was 146 μm). The average CRT at month 18 for the group in whom eAMD developed (n = 17) was 136 μm, and for the rest of the study population (n = 176), the CRT was 112 μm.

Fluorescein Angiography

The CRC defined the presence of MNV on FA by the presence of late leakage, staining, or both. At the time of diagnosis of new-onset eAMD, 17 of 26 patients (65%) had undergone FA.

Table 1. Rates of Investigator-Determined Exudative Age-Related Macular Degeneration in the Study Eye and History of Fellow-Eye Exudative Age-Related Macular Degeneration at Baseline in the FILLY Trial

Treatment	Total No. of Study Eyes Demonstrating Exudative Age-Related Macular Degeneration	No. of Study Eyes Demonstrating Exudative Age-Related Macular Degeneration without Fellow-Eye Exudative Age-Related Macular Degeneration	No. of Study Eyes Demonstrating Exudative Age-Related Macular Degeneration with Fellow-Eye Exudative Age-Related Macular Degeneration	*P* Value
Pegcetacoplan monthly (n = 86)	18/86 (20.9%)	6/50 (12.0%)	12/36 (33.3%)	0.0164*
Pegcetacoplan EOM (n = 79)	7/79 (8.9%)	2/51 (3.9%)	5/28 (17.9%)	0.0902†
Sham control (n = 81)	1/81 (1.2%)	1/52 (1.9%)	0/29 (0%)	1.0000†

EOM = every other month.
*Pearson chi-square test.
†Fisher exact test.

Table 2. Proportion of Study Eyes with a Double-Layer Sign at Baseline Demonstrating Exudative Age-Related Macular Degeneration by Month 18 in the FILLY Trial

Treatment	No. of Study Eyes with Double-Layer Sign at Baseline*	No. of Study Eyes Demonstrating Exudative Age-Related Macular Degeneration	Proportion of Study Eyes with Double-Layer Sign Not Demonstrating Exudative Age-Related Macular Degeneration	Proportion of Study Eyes with Double-Layer Sign Demonstrating Exudative Age-Related Macular Degeneration	Proportion of Study Eyes without Double-Layer Sign Not Demonstrating Exudative Age-Related Macular Degeneration	Proportion of Study Eyes without Double-Layer Sign Demonstrating Exudative Age-Related Macular Degeneration	*P* Value
All groups (n = 241)	89/241 (36.9%)	26/246 (10.6%)	70/89 (78.7%)	19/89 (21.3%)	145/152 (95.4%)	7/152 (4.6%)	<0.0001†
Pegcetacoplan monthly (n = 86)	40/85 (47.1%)	18/86 (20.9%)	28/40 (70%)	12/40 (30%)	39/45 (86.7%)	6/45 (13.3%)	0.0605†
Pegcetacoplan EOM (n = 79)	25/75 (33.3%)	7/79 (8.9%)	19/25 (76%)	6/25 (24%)	49/50 (98%)	1/50 (2%)	0.0047‡
Sham control (n = 81)	24/81 (29.6%)	1/81 (1.2%)	23/24 (95.8%)	1/24 (4.2%)	57/57 (100%)	0/57 (0%)	0.2963‡

EOM = every other month.
*Proportions of eyes with available baseline spectral-domain OCT images.
†Pearson chi-square test (comparing proportion of study eyes with and without a double-layer sign demonstrating exudative age-related macular degeneration).
‡Fisher exact test (comparing proportion of eyes with and without a double-layer sign demonstrating exudation).

Macular neovascularization was present in 10 of 17 patients (59%), all of whom were classified as having type 1 MNV, or occult lesions, and no FA evidence of MNV was found for 7 of 17 patients (41%). Among the 10 patients with confirmed MNV at the time of eAMD diagnosis and excluding 2 patients who received a diagnosis of eAMD at the month 18 visit, 7 patients had undergone FA at month 18 and 1 showed evidence of MNV, whereas 6 patients did not show evidence of MNV. Among the 7 patients with FA, but with no confirmed MNV at the time of eAMD diagnosis, excluding 1 patient who received a diagnosis of eAMD at the month 18 visit, 5 patients underwent FA at month 18, and none showed evidence of MNV.

Relationship between Fluorescein Angiography and Structural OCT Anatomic Changes

Among the 10 patients who showed detectable MNV on FA at the time of eAMD diagnosis, 9 patients had structural OCT data at the same visit, and all 9 patients showed cystoid spaces, SRF, or both on OCT imaging. Of the 7 patients who showed no detectable MNV on FA at eAMD diagnosis, 4 patients had structural OCT data at the same visit, and all 4 patients showed cystoid spaces, SRF, or both. Of the remaining 9 patients with no FA data at eAMD diagnosis, 8 patients had structural OCT data at eAMD diagnosis, and all 8 patients showed either cystoid spaces, SRF, or both. Among 19 patients with eAMD who showed a DLS at baseline, 12 patients had FA data at eAMD diagnosis, of whom 10 patients showed type 1 MNV and 2 patients showed no detectable MNV. Of the 7 patients with eAMD without a DLS at baseline, 5 patients had FA data at eAMD diagnosis, and none showed MNV.

Visual Acuity Outcomes

Best-corrected visual acuity data were not available for all 26 patients at the time of eAMD diagnosis. Thirteen patients had BCVA data from all 4 time points of interest. The mean BCVA results among these 13 patients are as follows: 61 letters (range, 32−83 letters) at study baseline, 54 letters (range, 10−82 letters) at the visit before eAMD diagnosis, 51 letters (range, 11−76 letters) at eAMD diagnosis, and 49 letters (range, 14−81 letters) at the final or month 18 visit.

The mean baseline BCVA letter score for patients who demonstrated eAMD (n = 26) was 65 letters (range, 32−85 letters), higher compared with patients who did not demonstrate eAMD (n = 220; mean, 59 letters [range, 23−88 letters]). The mean change in BCVA at diagnosis of eAMD from the visit before the event (n = 22) was −2.3 letters (range, −19 to 9 letters). The mean change in BCVA at month 18 compared with baseline (n = 17) was −11 letters (range, −50 to 6 letters), more than the mean change in BCVA among patients who did not demonstrate eAMD (n = 176), which was −6 letters (range, −63 to 22 letters). However, this difference may be explained by patients who lost vision before eAMD developed, because the mean change in BCVA from baseline to the visit before the eAMD diagnosis was −5 letters (range, −48 to 12 letters). Figure 4 shows patient-level BCVA data for all time points of interest as paired waterfall plots alongside observed CRT changes. Figure 5 summarizes patient-level findings of cystoid spaces, SRF, and MNV on FA at the corresponding time points.

Discussion

Monthly and EOM intravitreal injections of pegcetacoplan, an inhibitor of complement C3 cleavage, were shown to slow the enlargement rate of GA in a dose-dependent

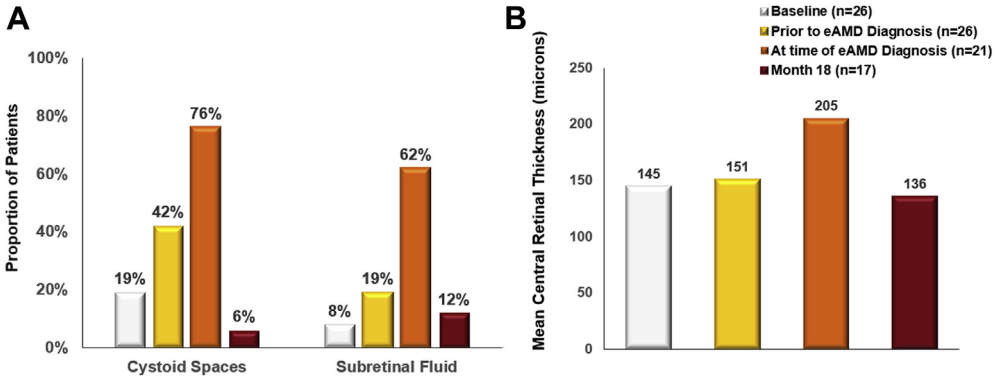


Figure 3. Bar graph showing retinal anatomic changes based on OCT images in patients with new-onset exudative age-related macular degeneration (eAMD) in the study eye during the FILLY trial. **A**, Percent of eyes with cystoid spaces or subretinal fluid at baseline, at the protocol-scheduled visit immediately before the eAMD diagnosis, at the time of eAMD diagnosis, and at the month 18 visit. **B**, Mean central retinal thickness measurements at baseline, at the protocol-scheduled visit immediately before the eAMD diagnosis, at the time of eAMD diagnosis, and at the month 18 visit.

manner when compared with sham injections in the phase 2 FILLY trial.[16] In addition, a dose-dependent increase in the incidence of new-onset, investigator-determined eAMD was observed. The outcome of the primary efficacy analysis in the FILLY trial was not affected adversely by the study eyes in which new-onset eAMD developed, and sensitivity analyses demonstrated that the primary end point, which was the change from baseline to month 12 using the difference in the square root GA lesion area measurements, was met when either including or excluding the data from patients with new-onset eAMD.[16] The current study identified 2 well-known factors that seemed to predispose study eyes to the development of eAMD: (1) presence of eAMD in the fellow eye and (2) DLS in the study eye.

The presence of eAMD in the fellow eye as a predisposing factor to exudation in the study eye is well recognized.[19–23] Although other large studies evaluating therapeutic candidates for GA therefore historically have excluded patients with a history of eAMD in the fellow eye,[24] this was not the case for the FILLY trial, which was designed to represent the real-world scenario of many AMD patients.[19] Noteworthy is that in the FILLY study, the number of patients with a history of eAMD in the fellow eye seemed to be disproportionately larger compared with the natural prevalence (37% vs. 22%),[19] possibly attributable to concurrent studies recruiting only patients with bilateral GA. A recent phase 2b trial investigating intravitreal injections of avacincaptad pegol (Zimura; Iveric Bio), an inhibitor of complement C5 cleavage, also excluded patients with a history of fellow-eye eAMD at baseline.[25]

A DLS in the study eye on baseline structural OCT as a predictive feature of new-onset eAMD is particularly interesting because it could imply that type 1 MNV located between Bruch's membrane and the RPE may have been present at baseline, although they did not manifest as occult MNV on FA at baseline. Although treatment-naïve nonexudative MNV can be identified reliably using indocyanine green angiography and OCT angiography (OCTA),[26–28] structural B-scans from spectral-domain OCT images also can be used to detect these lesions because most subclinical MNV appear as nonexudative type 1 MNV that can be detected by the presence of a DLS, which corresponds to a shallow irregular elevation of the RPE (SIRE).[17,29] A recent histopathologic study, albeit small, reported that thick basal laminar deposits can appear as DLS or SIRE signs on highly averaged OCT B-scans, and these findings on structural OCT imaging do not correspond to nonexudative type 1 MNV; however, the appearance of these nonneovascular lesions represent a minority of DLS or SIRE signs, as shown by the high sensitivity and specificity analyses performed on eyes with dry, nonexudative AMD in which the presence or absence of neovascularization was confirmed by swept-source OCTA.[17,30] Although subtle differences exist between the OCT findings of DLS and SIRE findings with and without neovascularization, such as the internal reflectivity of the lesion, we agree that some of the DLS and SIRE findings in this report might have been nonneovascular, but that does not diminish the association that we found in general between these lesions and exudation nor the specific association that most of these OCT findings are neovascular. The use of OCTA would be needed in the future specifically to classify these lesions.

On masked review of structural OCT images from the entire FILLY study population, 37% of baseline study eyes were found to harbor a DLS, thus suggesting the presence of pre-existing subclinical MNV, which was not an exclusionary criterion per study protocol. Multiple histopathologic studies have described the presence of nonexudative MNV in eyes with AMD.[31–33] Furthermore, OCTA has identified an equal prevalence of treatment-naïve nonexudative MNV in the presence of intermediate AMD and late AMD with GA, and if present in eyes with nonexudative AMD, these eyes have a 14-fold increased risk of exudation developing over 2 years.[18] In the present study, although the higher rate of eAMD in the monthly treatment arm can be explained partly by its higher proportion of patients with baseline DLS, no DLS imbalance was observed between the EOM and sham treatment arms, which also showed an eAMD imbalance. It is also evident from the FA findings that although DLS

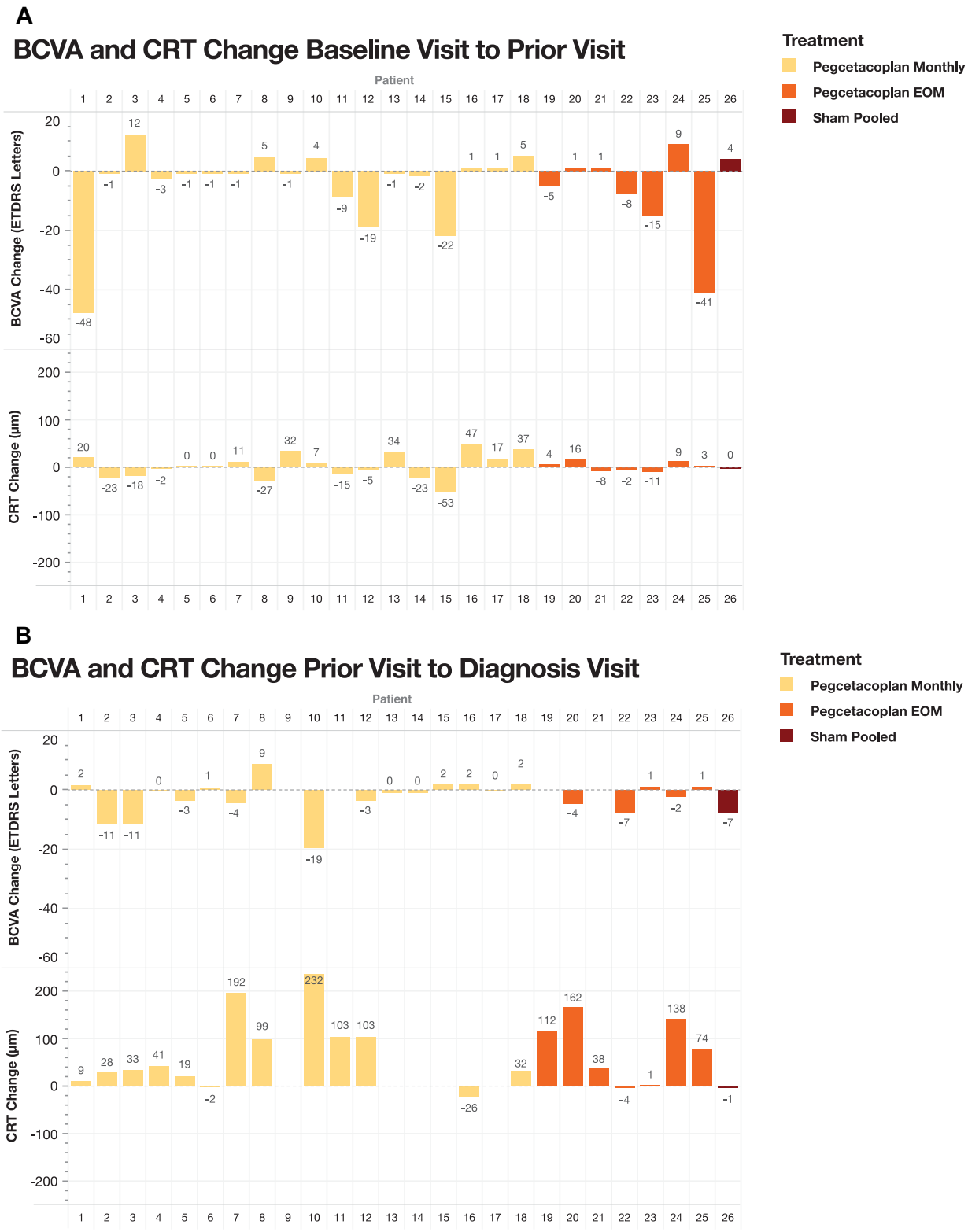
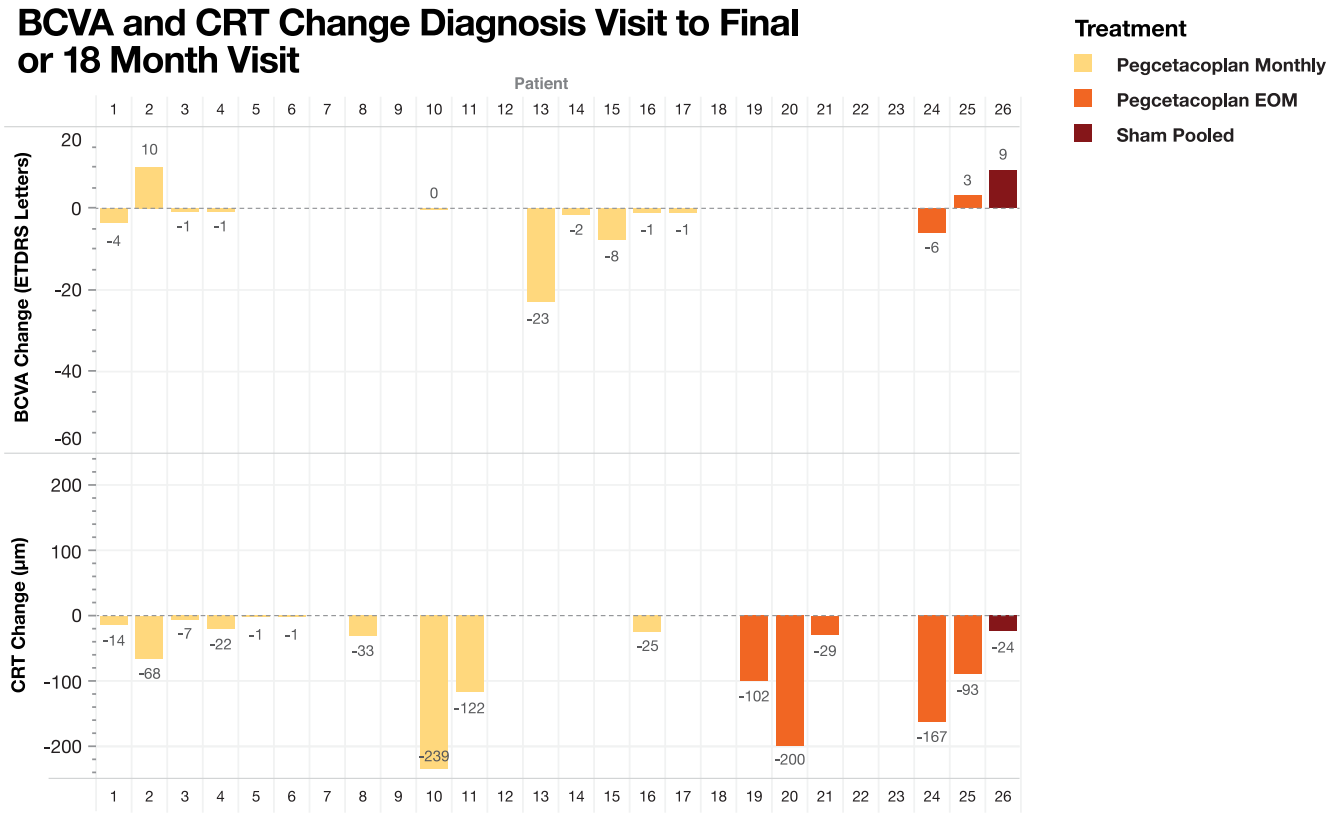


Figure 4. Bar graphs showing best-corrected visual acuity (BCVA) and central retinal thickness (CRT) changes in the study eye in patients with new-onset exudative age-related macular degeneration (eAMD) from the FILLY trial. **A**, From baseline to the protocol-scheduled visit immediately before eAMD diagnosis. **B**, From the protocol-scheduled visit immediately before eAMD diagnosis to the visit when eAMD was diagnosed. **C**, From the visit when eAMD was diagnosed to the final or month 18 visit. **D**, From the protocol-scheduled visit immediately before eAMD diagnosis to the final or month 18 visit. EOM = every other month; ETDRS = Early Treatment Diabetic Retinopathy Study.

C



D

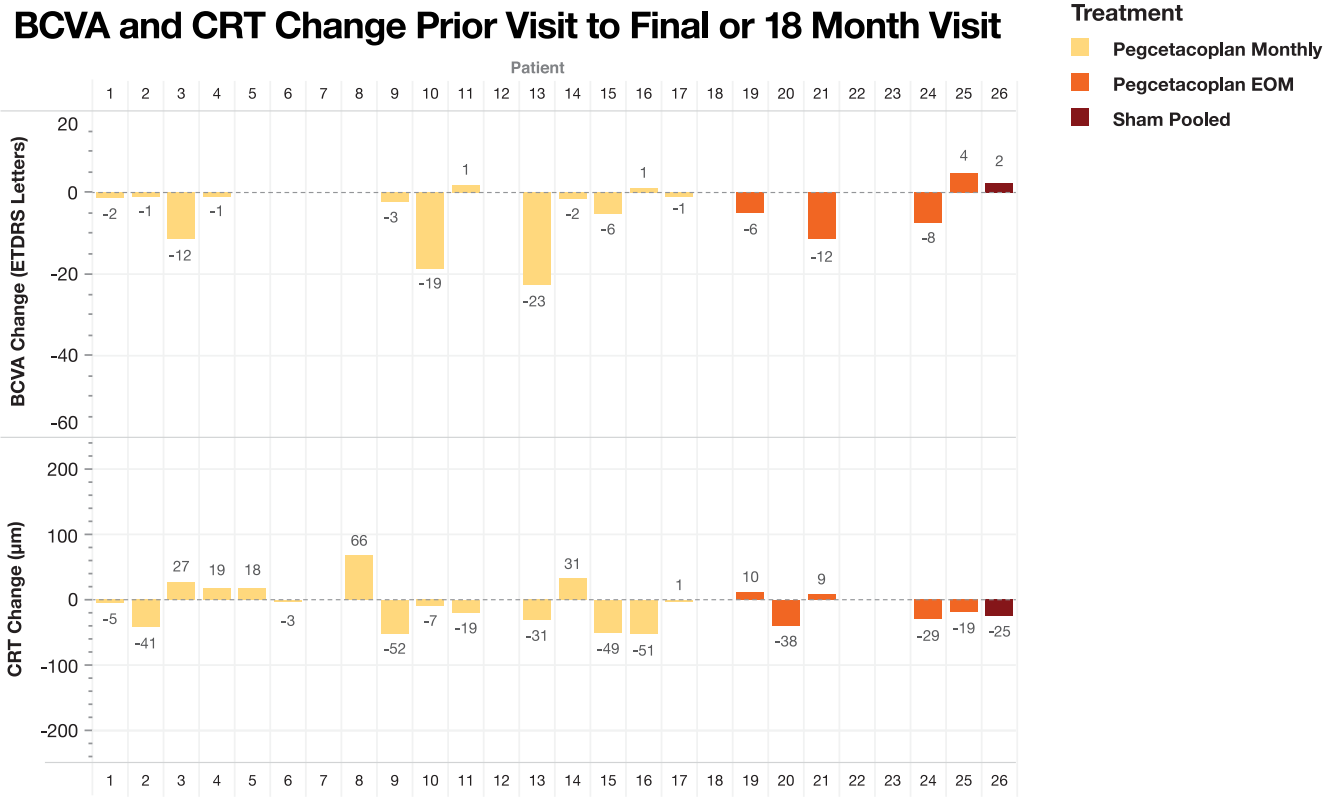
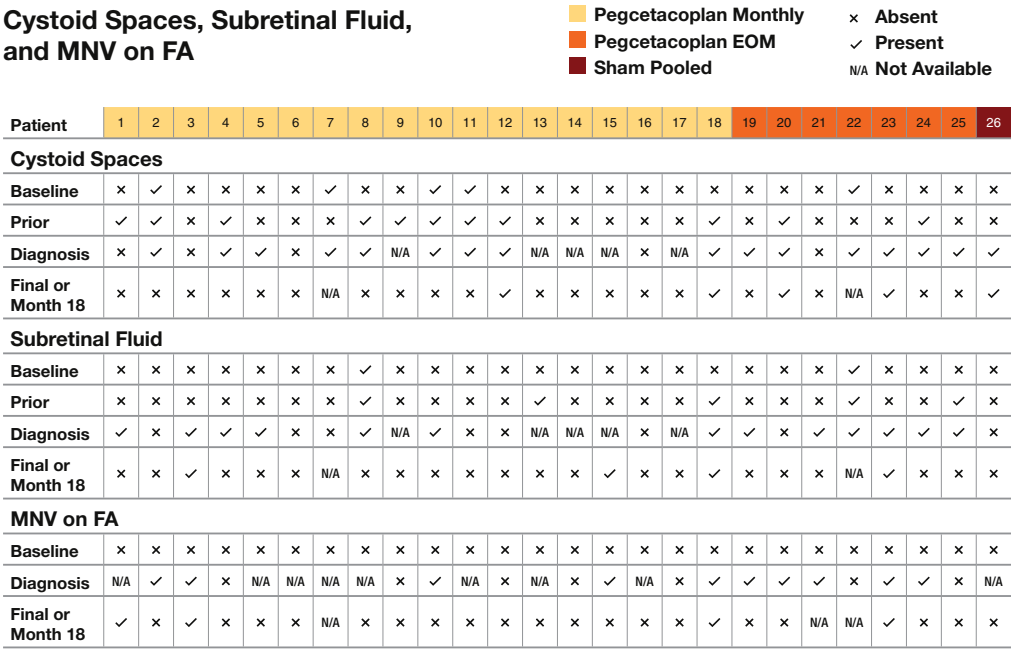


Figure 4. continue



Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Cystoid Spaces																										
Baseline	×	✓	×	×	×	×	✓	×	×	✓	✓	×	×	×	×	×	×	×	×	×	×	✓	×	×	×	×
Prior	✓	✓	×	✓	×	×	×	✓	✓	✓	✓	✓	×	×	×	×	×	✓	×	✓	×	×	×	✓	×	×
Diagnosis	×	✓	×	✓	✓	×	✓	✓	N/A	✓	✓	✓	N/A	N/A	N/A	×	N/A	✓	✓	✓	×	✓	✓	✓	✓	✓
Final or Month 18	×	×	×	×	×	×	N/A	×	×	×	×	✓	×	×	×	×	×	✓	×	✓	×	N/A	✓	×	×	✓
Subretinal Fluid																										
Baseline	×	×	×	×	×	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	✓	×	×	×	×
Prior	×	×	×	×	×	×	×	✓	×	×	×	×	✓	×	×	×	×	✓	×	×	×	✓	×	×	✓	×
Diagnosis	✓	×	✓	✓	✓	×	×	✓	N/A	✓	×	×	N/A	N/A	N/A	×	N/A	✓	✓	×	✓	✓	✓	✓	✓	×
Final or Month 18	×	×	✓	×	×	×	N/A	×	×	×	×	×	×	×	✓	×	×	✓	×	×	×	N/A	✓	×	×	×
MNV on FA																										
Baseline	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Diagnosis	N/A	✓	✓	×	N/A	N/A	N/A	N/A	×	✓	N/A	×	N/A	×	✓	N/A	×	✓	✓	✓	✓	×	✓	✓	×	N/A
Final or Month 18	✓	×	✓	×	×	×	N/A	×	×	×	×	×	×	×	×	×	×	✓	×	×	N/A	N/A	✓	×	×	×

Figure 5. Diagram showing subject-level findings of cystoid spaces, subretinal fluid, and macular neovascularization (MNV) on fluorescein angiography (FA) in the study eye in patients with new-onset exudative age-related macular degeneration (eAMD) from the FILLY trial at the following time points, as available: baseline, the protocol-scheduled visit immediately before eAMD diagnosis, the visit at which eAMD was diagnosed, and the final or month 18 visit. EOM = every other month; N/A = not available.

may manifest as type 1 MNV in most cases, type 1 MNV may not be associated or detectable in all cases. Although specific reasons remain unknown, pegcetacoplan may have influenced the propensity of nonexudative type 1 MNV to develop exudation. Interestingly, type 1 MNV has been reported to be protective against the growth of GA,[34] although sensitivity analyses in the FILLY study revealed no difference in GA growth rates with or without including the patients diagnosed with new-onset eAMD.[16]

Taken together, these findings provide a phenotypic rationale for a higher-than-expected rate of new-onset exudation, but do not explain fully the imbalance between the active and the sham control arms. It is possible that the single masked nature of the FILLY trial could have led to some overreporting, as evident by patients without evidence of MNV on FA at the time of eAMD diagnosis. It is also possible that the inhibition of C3 cleavage with pegcetacoplan, through its effects on immunologic processes in the retina, may have contributed to a repair response associated with increased VEGF-driven exudation in a subset of patients. Multiple possible mechanisms could explain this phenomenon. First, one theoretical possibility, although the assessment of changes in DLS or other indicators of capillary growth were not documented in this study, is that by inhibiting C3 cleavage and slowing the progression of GA, the viable endothelium in the choriocapillaris adjacent to the GA lesion may sprout new vessels, which would manifest as eAMD in some patients. Next, as indicated by some patients with new-onset eAMD in the FILLY trial for whom no detectable MNV was present on FA, the exudative phenotype may be the result of RPE decompensation or RPE pump failure in which fluid accumulates in the absence of MNV.[35] A third possibility is that the complement system plays a role in maintaining a prophagocytic state of macrophages in eyes with GA, and inhibition of C3 cleavage may lead to a transient phase of proangiogenic macrophages when prophagocytic macrophages transition to a resting state.[36,37] The findings of this trial, although not directly related, also call for careful reconsideration of the previously proposed theory based on histopathologic findings and animal studies that complement overactivation via the alternative pathway (factor P, properdin) plays a role in eAMD and that complement inhibition may have a therapeutic role in treating eAMD.[38] More work is needed to elucidate further the possible mechanism(s) underlying the observed increased incidence of investigator-determined eAMD with pegcetacoplan treatment in the phase 2 FILLY trial.

From a safety perspective, an independent safety monitoring committee allowed the FILLY study to be completed without any interruption because the risk-to-benefit profile was deemed favorable as a result of the nature of exudations with no appreciable impact on visual acuity. Hence, no adjustment to the study enrollment criteria was made in the subsequent phase 3 clinical trials DERBY and OAKS, which are ongoing. Importantly, these studies are double-masked, and processes are in place to corroborate new-onset exudations to eliminate any potential bias. While the phase 3 trials do not require OCTA or indocyanine green angiography, it is a requirement that FA is performed at the time of any patient being suspected of having the disease, and reading center confirmation of eAMD is to be obtained

at the time of diagnosis. Also, unlike in the FILLY trial, should patients receive anti-VEGF treatment, double-masking will be maintained, and they will continue to receive treatment with pegcetacoplan or sham as determined by their randomized arm through the end of the study. In future studies, it will be important to investigate whether the need for anti-VEGF treatment in patients who demonstrate new-onset eAMD is temporary or chronic.

Finally, longstanding as well as emerging evidence suggests that eAMD and GA are overlapping clinical manifestations of a shared immunologic disease process.[31–33] In addition to explaining why some patients with GA demonstrate eAMD, this also may explain why up to 98% of patients with eAMD demonstrate macular atrophy over time, with poor visual outcomes in many patients.[39–42] It is important to explore the immunologic mechanisms that these overlapping clinical manifestations of AMD have in common to understand the fine balance that is required to manage this common disease clinically. Furthermore, if nonexudative MNV, a known risk factor for eAMD development, can be recognized clinically using the DLS on structural OCT or other imaging methods such as OCTA, then clinicians may be able to follow up and manage higher-risk patients as needed to optimize anatomic and visual outcomes.

The limitations of this retrospective, post hoc, subgroup analysis include the lack of a comprehensive imaging protocol at the time of eAMD diagnosis because these events were unexpected, especially the absence of FA, structural OCT, and OCTA imaging from all patients. Hence, this analysis included only patients with investigator-diagnosed eAMD not necessarily confirmed by the central reading center, and conversely excluded patients identified retrospectively to have eAMD by the reading center who neither were reported nor treated by investigators. Although structural OCT findings in patients with investigator-determined eAMD were reviewed retrospectively as part of this post hoc analysis, the diagnosis itself may or may not have been based on OCT findings. It is likely that small nonexudative MNV lesions associated with a DLS (those the size of typical druse) may have been missed on the current baseline review of structural OCT images.

Moreover, the variable management of these eyes with anti-VEGF therapy and the loss of follow-up for a few patients who were discontinued from the trial makes it challenging to draw definitive conclusions about the impact of eAMD on visual outcomes. Because active pegcetacoplan treatment was stopped when eAMD was diagnosed, the possible benefits or consequences of continued pegcetacoplan therapy among this population are unknown. In the ongoing phase 3 studies, these limitations are being addressed, detailed protocols have been implemented, and study drug will be continued along with anti-VEGF therapy if eAMD develops; this set-up will provide a larger platform for more detailed analyses and definitive answers regarding the underlying mechanisms.

In summary, intravitreal injections of pegcetacoplan slowed the rate of GA growth and were associated with an unexpected increased incidence of new-onset investigator-determined eAMD identified to be dose-dependent among pegcetacoplan-treated patients. The development of eAMD seems to be associated with the presence of baseline eAMD in the contralateral eye and nonexudative MNV in the study eye. The conversion of nonexudative MNV to exudative MNV in these eyes may have an immunologic basis, and further study of these hypotheses is being pursued in an ongoing global phase 3 program.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. 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 approval for the phase 2 FILLY study was obtained at each clinical site. The 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). All participants provided informed consent.

No animal subjects were included in this study.

Author Contributions:

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Analysis and interpretation: Wykoff, Rosenfeld, Waheed, Singh, Ronca, Slakter, Staurenghi, Monés, Baumal, Saroj, Metlapally, Ribeiro

Data collection: Wykoff, Rosenfeld, Waheed, Metlapally, Ribeiro

Obtained funding: Wykoff, Singh, Slakter, Staurenghi, Monés, Saroj; Metlapally, Ribeiro, and Ronca are employees of Apellis Pharmaceuticals, and the study was performed as part of their regular employment duties.

Overall responsibility: Wykoff, Rosenfeld, Waheed, Singh, Ronca, Slakter, Staurenghi, Monés, Baumal, Saroj, Metlapally, Ribeiro

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CRC** = central reading center; **CRT** = central retinal thickness; **DLS** = double-layer sign; **eAMD** = exudative age-related macular degeneration; **EOM** = every other month; **FA** = fluorescein angiography; **GA** = geographic atrophy; **MNV** = macular neovascularization; **OCTA** = OCT angiography; **RPE** = retinal pigment epithelium; **SIRE** = shallow irregular elevation of the retinal pigment epithelium; **SRF** = subretinal fluid; **VEGF** = vascular endothelial growth factor.

Keywords:
Age-related macular degeneration, Complement, Double-layer sign, Exudation, Geographic atrophy, Macular neovascularization.

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References

1. Fritsche LG, Igl W, Bailey JN, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet*. 2016;48(2):134—143.
2. Yates JR, Sepp T, Matharu BK, et al. Complement C3 variant and the risk of age-related macular degeneration. *N Engl J Med*. 2007;357(6):553—561.
3. Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, et al. The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. *Retina*. 2017;37(5):819—835.
4. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990—2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(12):e1221—e1234.
5. Ferris 3rd FL, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120(4):844—851.
6. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079—1091.
7. Barbazetto I, Burdan A, Bressler NM, et al. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment—TAP and VIP report no. 2. *Arch Ophthalmol*. 2003;121(9):1253—1268.
8. Holz FG, Sadda SR, Busbee B, et al. Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration: Chroma and Spectri phase 3 randomized clinical trials. *JAMA Ophthalmol*. 2018;136(6):666—677.
9. Spaide RF, Jaffe GJ, Sarraf D, et al. Consensus nomenclature for reporting neovascular age-related macular degeneration data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. *Ophthalmology*. 2020;127(5):616—636.
10. Finger RP, Daien V, Eldem BM, et al. Anti-vascular endothelial growth factor in neovascular age-related macular degeneration—a systematic review of the impact of anti-VEGF on patient outcomes and healthcare systems. *BMC Ophthalmol*. 2020;20(1):294.
11. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537—2548.
12. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419—1431.
13. Gillies MC, Campain A, Barthelmes D, et al. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. *Ophthalmology*. 2015;122(9):1837—1845.
14. Gune S, Abdelfattah NS, Karamat A, et al. Spectral-domain OCT-based prevalence and progression of macular atrophy in

the HARBOR Study for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(4):523–532.
15. Heier JS, Pieramici D, Chakravarthy U, et al. Visual function decline resulting from geographic atrophy: results from the Chroma and Spectri phase 3 trials. *Ophthalmol Retina*. 2020;4(7):673–688.
16. 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.
17. Shi Y, Motulsky EH, Goldhardt R, et al. Predictive value of the OCT double-layer sign for identifying subclinical neovascularization in age-related macular degeneration. *Ophthalmol Retina*. 2019;3(3):211–219.
18. Yang J, Zhang Q, Motulsky EH, et al. Two-year risk of exudation in eyes with nonexudative age-related macular degeneration and subclinical neovascularization detected with swept source optical coherence tomography angiography. *Am J Ophthalmol*. 2019;208:1–11.
19. Chew EY, Clemons TE, Agron E, et al. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA Ophthalmol*. 2014;132(3):272–277.
20. Chakravarthy U, Bailey CC, Johnston RL, et al. Characterizing disease burden and progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2018;125(6):842–849.
21. Chakravarthy U, Bailey CC, Scanlon PH, et al. Progression from early/intermediate to advanced forms of age-related macular degeneration in a large UK cohort: rates and risk factors. *Ophthalmol Retina*. 2020;4(7):662–672.
22. 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.
23. Yim J, Chopra R, Spitz T, et al. Predicting conversion to wet age-related macular degeneration using deep learning. *Nat Med*. 2020;26(6):892–899.
24. 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.
25. 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;128:576–586.
26. Hanutsaha P, Guyer DR, Yannuzzi LA, et al. Indocyanine-green videoangiography of drusen as a possible predictive indicator of exudative maculopathy. *Ophthalmology*. 1998;105(9):1632–1636.
27. Laiginhas R, Yang J, Rosenfeld PJ, Falcão M. Nonexudative macular neovascularization—a systematic review of prevalence, natural history, and recent insights from OCT angiography. *Ophthalmol Retina*. 2020;4(7):651–661.
28. Schneider U, Gelisken F, Inhoffen W, Kreissig I. Indocyanine green angiographic findings in fellow eyes of patients with unilateral occult neovascular age-related macular degeneration. *Int Ophthalmol*. 1997;21(2):79–85.
29. Narita C, Wu Z, Rosenfeld PJ, et al. Structural OCT signs suggestive of subclinical nonexudative macular neovascularization in eyes with large drusen. *Ophthalmology*. 2020;127(5):637–647.
30. Sura AA, Chen L, Messinger JD, et al. Measuring the contributions of basal laminar deposit and Bruch's membrane in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2020;61(13):19.
31. Green WR, Key 3rd SN. Senile macular degeneration: a histopathologic study. *Trans Am Ophthalmol Soc*. 1977;75:180–254.
32. Sarks SH. Ageing and degeneration in the macular region: a clinico-pathological study. *Br J Ophthalmol*. 1976;60(5):324–341.
33. Kaszubski P, Ben Ami T, Saade C, Smith RT. Geographic atrophy and choroidal neovascularization in the same eye: a review. *Ophthalmic Res*. 2016;55(4):185–193.
34. Dhrami-Gavazi E, Balaratnasingam C, Lee W, Freund KB. Type 1 neovascularization may confer resistance to geographic atrophy amongst eyes treated for neovascular age-related macular degeneration. *Int J Retina Vitreous*. 2015;1:15.
35. Hilely A, Au A, Freund KB, et al. Non-neovascular age-related macular degeneration with subretinal fluid. *Br J Ophthalmol*. 2020 Sep 12;bjophthalmol-2020-317326. https://doi.org/10.1136/bjophthalmol-2020-317326. Online ahead of print.
36. Cao X, Shen D, Patel MM, et al. Macrophage polarization in the maculae of age-related macular degeneration: a pilot study. *Pathol Int*. 2011;61(9):528–535.
37. Tarique AA, Logan J, Thomas E, et al. Phenotypic, functional, and plasticity features of classical and alternatively activated human macrophages. *Am J Respir Cell Mol Biol*. 2015;53(5):676–688.
38. Wolf-Schnurrbusch UE, Stuck AK, Hess R, et al. Complement factor P in choroidal neovascular membranes of patients with age-related macular degeneration. *Retina*. 2009;29(7):966–973.
39. Bhisitkul RB, Mendes TS, Rofagha S, et al. Macular atrophy progression and 7-year vision outcomes in subjects from the ANCHOR, MARINA, and HORIZON studies: the SEVEN-UP study. *Am J Ophthalmol*. 2015;159(5):915–924 e2.
40. Jaffe GJ, Ying GS, Toth CA, et al. Macular morphology and visual acuity in year five of the Comparison of Age-related Macular Degeneration Treatments Trials. *Ophthalmology*. 2019;126(2):252–260.
41. Rofagha S, Bhisitkul RB, Boyer DS, et al. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology*. 2013;120(11):2292–2299.
42. Sadda SR, Tuomi LL, Ding B, et al. Macular atrophy in the HARBOR study for neovascular age-related macular degeneration. *Ophthalmology*. 2018;125(6):878–886.