



Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials

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Summary

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Background Geographic atrophy is a leading cause of progressive, irreversible vision loss. The objectives of OAKS and DERBY were to assess the efficacy and safety of pegcetacoplan compared with sham treatment in patients with geographic atrophy.

Methods OAKS and DERBY were two 24-month, multicentre, randomised, double-masked, sham-controlled, phase 3 studies, in which patients aged 60 years and older with geographic atrophy secondary to age-related macular degeneration were enrolled at 110 clinical sites and 122 clinical sites worldwide, respectively. Patients were randomly assigned (2:2:1:1) by central web-based randomisation system to intravitreal 15 mg per 0.1 mL pegcetacoplan monthly or every other month, or sham monthly or every other month using stratified permuted block randomisation (stratified by geographic atrophy lesion area at screening, history or presence of active choroidal neovascularisation in the eye not under assessment, and block size of six). Study site staff, patients, reading centre personnel, evaluating physicians, and the funder were masked to group assignment. Sham groups were pooled for the analyses. The primary endpoint was the change from baseline to month 12 in the total area of geographic atrophy lesions in the study eye based on fundus autofluorescence imaging, in the modified intention-to-treat population (ie, all patients who received one or more injections of pegcetacoplan or sham and had a baseline and at least one post-baseline value of lesion area). Key secondary endpoints (measured at 24 months) were change in monocular maximum reading speed of the study eye, change from baseline in mean functional reading independence index score, change from baseline in normal luminance best-corrected visual acuity score, and change from baseline in the mean threshold sensitivity of all points in the study eye by mesopic microperimetry (OAKS only). Safety analyses included patients who were randomly assigned and received at least one injection of pegcetacoplan or sham. The now completed studies are registered with ClinicalTrials.gov, NCT03525613 (OAKS) and NCT03525600 (DERBY).

Findings Between Aug 30, 2018, and July 3, 2020, 1258 patients were enrolled in OAKS and DERBY. The modified intention-to-treat populations comprised 614 (96%) of 637 patients in OAKS (202 receiving pegcetacoplan monthly, 205 pegcetacoplan every other month, and 207 sham) and 597 (96%) of 621 patients in DERBY (201 receiving pegcetacoplan monthly, 201 pegcetacoplan every other month, and 195 sham). In OAKS, pegcetacoplan monthly and pegcetacoplan every other month significantly slowed geographic atrophy lesion growth by 21% (absolute difference in least-squares mean -0.41 mm^2 , 95% CI -0.64 to -0.18 ; $p=0.0004$) and 16% (-0.32 mm^2 , -0.54 to -0.09 ; $p=0.0055$), respectively, compared with sham at 12 months. In DERBY, pegcetacoplan monthly and pegcetacoplan every other month slowed geographic atrophy lesion growth, although it did not reach significance, by 12% (-0.23 mm^2 , -0.47 to 0.01 ; $p=0.062$) and 11% (-0.21 mm^2 , -0.44 to 0.03 ; $p=0.085$), respectively, compared with sham at 12 months. At 24 months, pegcetacoplan monthly and pegcetacoplan every other month slowed geographic atrophy lesion growth by 22% (-0.90 mm^2 , -1.30 to -0.50 ; $p<0.0001$) and 18% (-0.74 mm^2 , -1.13 to -0.36 ; $p=0.0002$) in OAKS, and by 19% (-0.75 mm^2 , -1.15 to -0.34 ; $p=0.0004$) and 16% (-0.63 mm^2 , -1.05 to -0.22 ; $p=0.0030$) in DERBY, respectively, compared with sham. There were no differences in key secondary visual function endpoints at 24 months. Serious ocular treatment-emergent adverse events were reported in five (2%) of 213, four (2%) of 212, and one (<1%) of 211 patients in OAKS, and in four (2%) of 206, two (1%) of 208, and two (1%) of 206 patients in DERBY receiving pegcetacoplan monthly, pegcetacoplan every other month, and sham, respectively, at 24 months. New-onset exudative age-related macular degeneration was reported in 24 (11%), 16 (8%), and four (2%) patients in OAKS, and in 27 (13%), 12 (6%), and nine (4%) patients in DERBY receiving pegcetacoplan monthly, pegcetacoplan every other month, and sham, respectively, at 24 months.

Interpretation Pegcetacoplan, the first treatment approved by the US Food and Drug Administration for geographic atrophy, slowed geographic atrophy lesion growth with an acceptable safety profile.

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Introduction

Geographic atrophy is an advanced form of age-related macular degeneration (AMD) characterised by the loss of photoreceptors, retinal pigment epithelium, and choriocapillaris, resulting in severe, irreversible vision loss in people aged 60 years or older worldwide.^{1,2} Geographic atrophy results in a high burden of illness, with quality of life severely reduced for patients and their caregivers.^{1,4} Consequences of visual impairment include increased fall risk, difficulty in reading, driving, and recognising faces, and ultimately loss of independence.^{4,5} In February, 2023, pegcetacoplan was approved by the US Food and Drug Administration (FDA) as the first and only treatment for geographic atrophy secondary to AMD.⁶

Overactivation of the complement system is implicated in the pathogenesis of geographic atrophy,⁷ and genome-wide association studies have found strong associations between genetic polymorphisms in the complement pathways and AMD risk, although the association between the complement system and geographic atrophy expansion is being evaluated.⁸ Dysregulation of these complement proteins results in chronic inflammation, opsonisation of cells, and further amplification of the alternative complement pathway, all of which promote

retinal cell death.^{9–11} C3, the most abundant complement protein and the point at which all three complement pathways converge, is spontaneously cleaved into C3a and C3b.¹² C3 might be an advantageous therapeutic target because its effects span across all complement activation pathways and because of the heterogeneity of geographic atrophy phenotypes and accompanying genetic polymorphisms associated with geographic atrophy.

Pegcetacoplan targets C3 and C3b, and it might broadly regulate the deleterious complement-mediated effector functions to improve cell survival and reduce vascular loss.^{9,10} Pegcetacoplan has been approved by the FDA and the European Medicines Agency for systemic use in the treatment of paroxysmal nocturnal haemoglobinuria, a life-threatening complement-mediated blood disorder.^{14,15} Intravitreal administration of pegcetacoplan was evaluated in geographic atrophy in the phase 2 FILLY trial, in which pegcetacoplan monthly and pegcetacoplan every other month significantly reduced geographic atrophy lesion growth compared with sham.¹³ In the OAKS and DERBY phase 3 studies, we assessed the efficacy and safety of intravitreal pegcetacoplan compared with sham for the treatment of geographic atrophy secondary to AMD.

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See Online for appendix 1

Research in context

Evidence before this study

Geographic atrophy is an advanced form of age-related macular degeneration resulting in substantial vision loss. We searched PubMed for articles published in English from Jan 1, 2022, to Aug 15, 2023, using the terms “geographic atrophy AND progression AND age-related macular degeneration NOT neovascular age-related macular degeneration”. The term “neovascular AMD” and case reports were excluded. Our search identified 56 publications. Until the approval of pegcetacoplan, no treatment was available. Although overactivation of the complement system has been implicated in the pathogenesis of geographic atrophy, its association with geographic atrophy expansion is being evaluated. Investigational compounds targeting the alternative complement pathway have not slowed progression of geographic atrophy. Findings reported from a phase 2 study with pegcetacoplan, which targets complement factors C3 and C3b to suppress the downstream effects of excessive complement activation, showed significantly slowed growth of geographic atrophy lesions in patients receiving pegcetacoplan compared with those in the sham group.

Added value of this study

We report the results of two phase 3 randomised controlled studies, OAKS and DERBY, investigating the efficacy and safety of intravitreal pegcetacoplan in patients with geographic atrophy. To our knowledge, OAKS is the first phase 3 study in patients with geographic atrophy to meet its primary endpoint with a statistically significant difference in geographic atrophy lesion growth at 12 months with pegcetacoplan compared with sham. Although the 12-month primary endpoint was not met in DERBY, the treatment effects in the combined studies increased over time.

Implications of all the available evidence

These findings are, to our knowledge, the first phase 3 data to support the complement system as an appropriate target in the treatment of geographic atrophy, showing that pegcetacoplan can slow the progression of geographic atrophy. The recent US Food and Drug Administration approval of pegcetacoplan provides patients with geographic atrophy with a treatment option for the first time.

Methods

Study design

See Online for appendix 2

OAKS and DERBY were similar 24-month, multicentre, randomised, double-masked, sham-controlled, phase 3 studies, which enrolled patients at 110 clinical sites and 122 clinical sites worldwide, respectively (appendix 1 pp 4–9). OAKS and DERBY were designed as confirmatory trials for regulatory purposes. Study protocols were approved by institutional review boards or ethics committees at each site. Both studies adhered to the Declaration of Helsinki. The protocols of both studies are available in appendix 2. The clinical programme was placed on hold in October, 2018, because of a drug impurity, and resumed in March, 2019, after the impurity had been removed.

Patients

In both studies, eligible patients were aged 60 years or older. Patients were included if their eye under treatment assessment (henceforth referred to as study eye) had best-corrected visual acuity of 24 letters or better on Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Snellen chart equivalent of 20/320 or better); if they had a diagnosis of geographic atrophy secondary to AMD, confirmed by the reading centre; and if the total geographic atrophy area was 2.5–17.5 mm² or—if multifocal—at least one lesion was 1.25 mm² or larger on fundus autofluorescence (FAF) imaging. Non-subfoveal and subfoveal study eye lesions were allowed. For patients with bilateral geographic atrophy in whom both eyes met the study entry criteria, the worse-seeing eye was designated as the study eye. In OAKS, patients were also required to be able to perform the microperimetry assessment, which was not required in DERBY because microperimetry was only assessed in OAKS. Patients were excluded if they had geographic atrophy secondary to a condition other than AMD and any history or presence of active choroidal neovascularisation (CNV) in the study eye, including any evidence of retinal pigment epithelium tears or neovascularisation elsewhere. A history or presence of active CNV in the eye not under treatment assessment (henceforth referred to as fellow eye) was not an exclusion criterion. The complete list of eligibility criteria is given in appendix 1 (p 16). Data on sex was self-reported by study participants. All patients provided written informed consent.

Randomisation and masking

In both studies, eligible patients were randomly assigned (2:2:1:1) to receive 15 mg per 0.1 mL intravitreal injection of pegcetacoplan monthly, 15 mg per 0.1 mL intravitreal injection of pegcetacoplan every other month, sham injection monthly, or sham injection every other month, for 24 months.

The randomisation method was a stratified permuted block randomisation. The stratification criteria were geographic atrophy lesion area at screening (<7.5 mm² vs

≥7.5 mm²), history or presence of active CNV in the fellow eye (yes vs no), and block size of six. A central web-based randomisation system was used to assign patients to treatment. Eligible patients' stratification factor details were entered into the randomisation system by a member of the clinical site, and on the basis of the stratification factors entered, the patient was allocated to the next available randomisation slot and assigned a treatment. For each injection visit, the randomisation system provided a kit number of an available investigational product kit at the site corresponding to the treatment assigned at randomisation to use for dosing. As both studies were double-masked, study site staff (assistants and pharmacists), patients, reading centre personnel, the assigned evaluating physicians, and the funder were masked to treatment assignment. However, the treating physician and any associated support staff involved in performing the intravitreal or sham injections were not masked to study treatment. Individuals who were unmasked were not allowed to discuss treatment and patient outcome with study staff who were masked, including the evaluating physician. The principal investigator was masked to patients' treatment assignment. Documentation was put in place to avoid unintentional unmasking during the study. All study roles were clearly documented on the site delegation of authority log. At 12 months, only the sponsor personnel responsible for analysing, interpreting, and reporting data were unmasked to treatment assignment. The success of masking was not formally assessed.

Procedures

In both studies, a screening period of up to 28 days was followed by 24 months of treatment. For the first 12 months, all patients returned every month to the clinical site. From month 12 onwards, patients receiving pegcetacoplan monthly or sham monthly continued attending the clinical site on a monthly basis whereas patients in the every-other-month groups attended the clinical site every other month. Pegcetacoplan was injected with a thin wall needle; its administration was allowed only when the intraocular pressure was 21 mm Hg or less. The procedure for the sham injections was the same as that used for the intravitreal injections of pegcetacoplan, except no actual injection occurred. Instead, the physician only touched the study eye with the blunt end of the syringe.

Study eyes that developed exudative AMD were treated concomitantly with pegcetacoplan and anti-vascular endothelial growth factor (VEGF), in accordance with the protocol. If anti-VEGF therapy was administered in the study eye on the same day as a pegcetacoplan (or sham) injection, the anti-VEGF therapy was administered first and the pegcetacoplan or sham injection occurred at least 30 min after the anti-VEGF injection and only when the intraocular pressure was 21 mm Hg or less. The decision to initiate anti-VEGF treatment was the sole responsibility

of the investigator, who was responsible for selecting either on-label ranibizumab (0.5 mg; 0.05 mL intravitreal administered as a single dose) or aflibercept (2 mg; 0.05 mL intravitreal administered as a single dose); ranibizumab was to be given monthly, whereas aflibercept was to be given every other month after three monthly loading doses.

FAF images were evaluated in a central reading centre by a minimum of two certified readers with independent manual measurements of features of the geographic atrophy lesions. If new exudation related to development of active CNV in the study eye was suspected by an investigator on the basis of fundus examination or optical coherence tomography findings (eg, subretinal fluid, intraretinal fluid, cystoid macular oedema, and serous pigment epithelial detachment), then fluorescein angiography, structural optical coherence tomography, and fundus photographs were obtained, together with optical coherence tomography angiography at sites where available. The reading centre prospectively assessed fluorescein angiography for all patients at baseline, month 12, and month 24. FAF imaging was done every 2 months, best-corrected visual acuity was measured at every study visit, and other functional outcomes were measured every 6 months.

An external, independent data monitoring committee reviewed all data across the conduct of the studies on an ongoing basis. The committee met every 6 months to do a masked review of all relevant events.

Outcomes

In both studies, the primary endpoint was change from baseline to month 12 in the total area of geographic atrophy lesions in the study eye based on FAF image analysis. Key secondary endpoints, which were prespecified to be analysed at 24 months, were monocular maximum reading speed of the study eye, as assessed by the Minnesota low vision reading chart or the Radner reading chart (depending on the country in which the assessment was done; OAKS and DERBY combined);^{16,17} functional reading independence index scores, with the index being a binocular measure (OAKS and DERBY combined);¹⁸ normal-luminance best-corrected visual acuity scores, as assessed by ETDRS charts (OAKS and DERBY combined);¹⁹ and change in mean threshold sensitivity, as assessed by mesopic microperimetry for the evaluation of the macular functional response (OAKS only).²⁰ Other prespecified secondary and subgroup analyses were change from baseline to month 24 in the National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) distance activity subscale score (ie, a binocular measure), total area of geographic atrophy lesions in the study eye at month 24, and change in lesion size stratified by subfoveal and non-subfoveal lesion location based on FAF imaging from baseline to month 24, all of which were assessed using data from the combined studies. For OAKS, we also report the findings of a

post-hoc analysis of change in the number of scotomatous points in the junctional zone of atrophy (ie, the region of the lesion with most active pathophysiological changes, defined as 250 µm inside and outside the border of the lesion) from baseline to month 24.

The main safety endpoints were the incidence and severity of ocular and systemic treatment-emergent adverse events (TEAEs) at months 12 and 24; TEAE grading is described in appendix 1 (p 10). Information on suspected new exudation related to the development of active CNV in the study eye is in appendix 1 (p 27).

Statistical analysis

Patients in the sham monthly and sham every-other-month groups were pooled into a single control group for all analyses (henceforth referred to as sham). Power calculations assumed an overall SD in change from baseline lesion area of 1.25 mm² per year (based on natural history calculations) and 1.50 mm² per year (based on FILLY data).^{12,21} For each study, a sample size of 600 patients (200 pegcetacoplan monthly, 200 pegcetacoplan every other month, 100 sham monthly, and 100 sham every other month) provided more than 99.9% (using natural history calculations) and 99.2% (using FILLY data) power to detect a difference in the change from baseline to month 12 in geographic atrophy lesion area of 0.66 mm² between pegcetacoplan monthly and sham. The same sample size had 92.9% (using natural history calculations) and 81.5% (using FILLY data) power to detect a difference of 0.43 mm² between pegcetacoplan every other month and sham. Power calculations were based on two-sided *t* tests at an α level of 0.0495. All efficacy analyses were done using the modified intention-to-treat population, which was defined in the statistical analysis plan finalised before study unmasking at month 12 as all patients who received one or more injections of pegcetacoplan or sham and had a baseline and at least one post-baseline value of geographic atrophy lesion area measured by FAF in the study eye. A mixed-effect model for repeated measures was used to measure the least-squares mean change from baseline to month 12 in the total area of geographic atrophy lesions, with no imputation for missing data (appendix 1 p 10). The same method was used to analyse the total area of geographic atrophy lesions at month 24. Prespecified analyses of combined OAKS and DERBY data were done for the lesion growth analyses at months 12 and 24 in the modified intention-to-treat population and in the subgroups with and without subfoveal geographic atrophy involvement at baseline. Piecewise rate of change post-hoc analyses were done for growth of geographic atrophy lesions to compare the slope of lesion growth with pegcetacoplan versus sham (appendix 1 p 10). We also did a post-hoc linear trend test using data from the combined studies, to further assess whether the treatment effects of pegcetacoplan monthly and pegcetacoplan every other month compared with sham

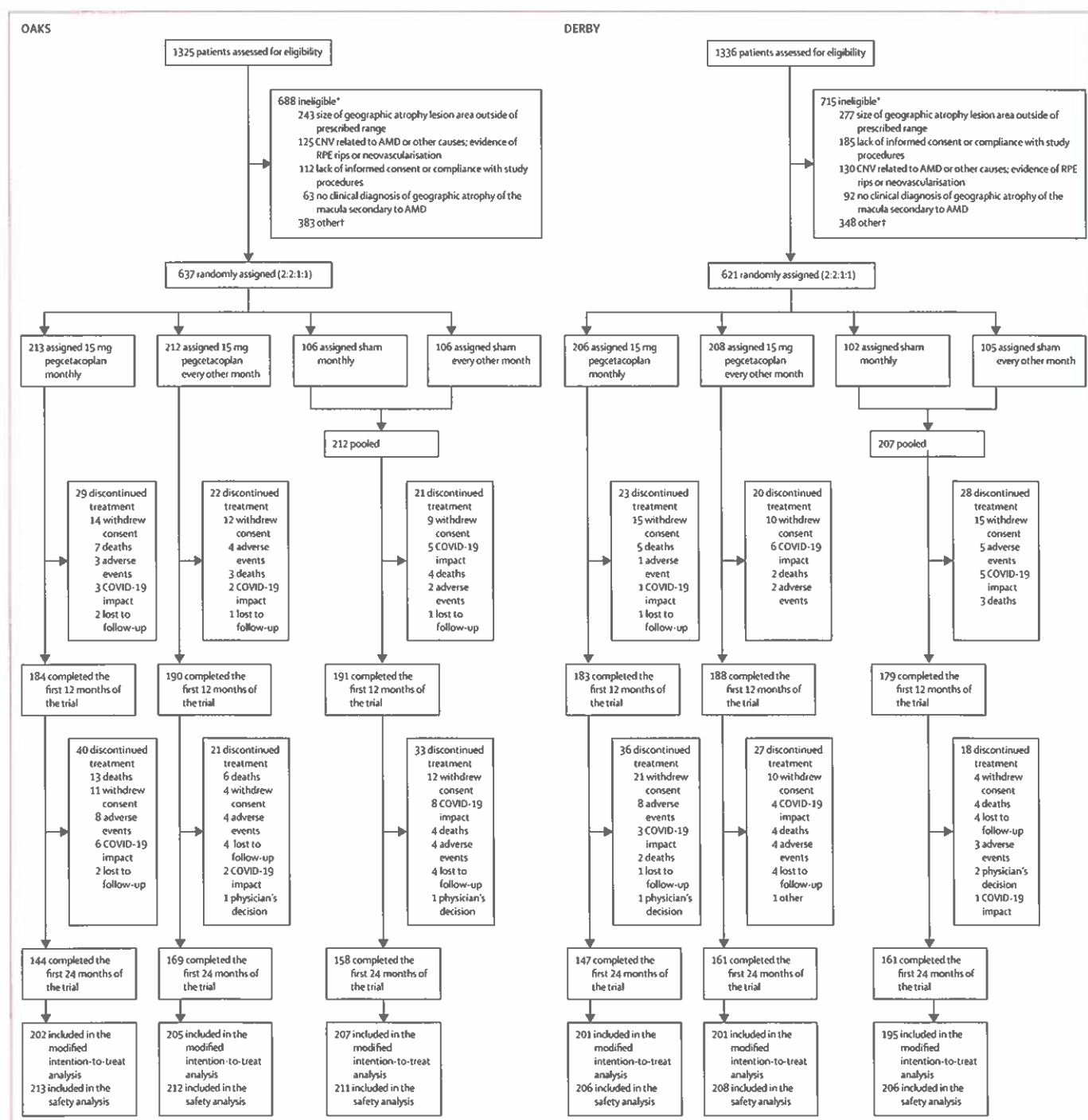


Figure 1: Trial profile

The modified intention-to-treat population included all patients who were randomly assigned, received one or more injections of pegcetacoplan or sham, and had a baseline and at least one post-baseline value of lesion area. The safety population included all patients who were randomly assigned and received at least one injection of pegcetacoplan or sham. CNV=choroidal neovascularisation. AMD=age-related macular degeneration. RPE=retinal pigment epithelium. *Individuals could be excluded for more than one reason. †Other reasons are listed in appendix 1 (p 14); ≥25 individuals met a specific criterion for exclusion.

increased over time within each of the 6-month periods until month 24. Key secondary endpoints and other secondary and subgroup analyses were prespecified to be analysed in the combined OAKS and DERBY studies, except for the macular sensitivity measurement, which was only evaluated in OAKS. Model descriptions for all outcomes are described in appendix 1 (pp 10–11).

Hypothesis testing in each study was done at a two-sided 0·0496 α level and multiplicity was controlled as described in appendix 1 (pp 10–11). p values from statistical tests not included in the preplanned hierarchy, even if the analyses themselves were prespecified, are labelled as nominal.

Preplanned sensitivity analyses at months 12 and 24 were control-based multiple imputation analyses for patients who discontinued the study for reasons

potentially related to study drug or lack of efficacy, tipping point analyses for study discontinuations, exclusion of geographic atrophy lesions with indeterminate boundary, and missed treatment due to COVID-19-related reasons. Additional post-hoc control-based multiple imputation sensitivity analyses were done to evaluate the impact of all study discontinuations and all-cause missing data at month 24.

Safety data were recorded at 12 months and 24 months for patients in the safety population, consisting of all patients who were randomly assigned and received one or more injections of pegcetacoplan or sham.

We did all statistical analyses using SAS, version 9.4. The studies are registered with ClinicalTrials.gov, NCT03525613 (OAKS) and NCT03525600 (DERBY).

	OAKS			DERBY		
	Pegcetacoplan monthly (n=202)	Pegcetacoplan every other month (n=205)	Sham (n=207)	Pegcetacoplan monthly (n=201)	Pegcetacoplan every other month (n=201)	Sham (n=195)
Age, years	78·8 (7·2)	78·1 (7·7)	78·6 (7·3)	78·7 (6·9)	79·2 (7·1)	78·6 (7·3)
Sex						
Female	125 (62%)	117 (57%)	133 (64%)	118 (59%)	120 (60%)	123 (63%)
Male	77 (38%)	88 (43%)	74 (36%)	83 (41%)	81 (40%)	72 (37%)
Geographical region						
USA	147 (73%)	142 (69%)	148 (71%)	142 (71%)	122 (61%)	122 (63%)
Rest of the world	55 (27%)	63 (31%)	59 (29%)	59 (29%)	79 (39%)	73 (37%)
Race						
Asian	3 (1%)	1 (0%)	2 (1%)	0	1 (0%)	0
Black or African American	2 (1%)	0	0	1 (<1%)	1 (0%)	0
White	185 (92%)	189 (92%)	188 (91%)	187 (93%)	186 (93%)	188 (96%)
Multiple	0	0	0	0	1 (<1%)	0
Not reported*	12 (6%)	12 (6%)	14 (7%)	12 (6%)	10 (5%)	6 (3%)
Unknown	0	3 (1%)	3 (1%)	1 (0%)	2 (1%)	1 (1%)
Ethnicity						
Hispanic or Latinx	4 (2%)	7 (3%)	4 (2%)	32 (16%)	35 (17%)	29 (15%)
Not Hispanic or Latinx	184 (91%)	186 (91%)	187 (90%)	158 (79%)	151 (75%)	160 (82%)
Not reported*	14 (7%)	12 (6%)	16 (8%)	10 (5%)	11 (5%)	6 (3%)
Unknown	0	0	0	1 (0%)	4 (2%)	0
Size of geographic atrophy lesion, mm ²	8·18 (3·89)	8·30 (3·90)	8·21 (3·71)	8·37 (4·18)	8·25 (3·89)	8·24 (4·26)
Size of geographic atrophy lesion <7·5 mm ²	101 (50%)	98 (48%)	104 (50%)	99 (49%)	98 (49%)	95 (49%)
Geographic atrophy lesion without subfoveal involvement	86 (43%)	74 (36%)	60 (29%)	72 (36%)	81 (40%)	73 (37%)
Unifocal geographic atrophy lesion	59 (29%)	62 (30%)	68 (33%)	54 (27%)	53 (26%)	66 (34%)
>20 intermediate or large drusen in the study eye†	93 (46%)	104 (51%)	104 (50%)	78 (39%)	78 (39%)	98 (50%)
Study eye NL-BCVA, ETDRS letters‡	61·0 (15·3)	58·2 (17·0)	57·6 (16·6)	59·5 (17·4)	58·7 (16·1)	59·0 (16·9)
Study eye LLD, ETDRS letters§	26·7 (16·8)	25·7 (17·6)	24·9 (17·4)	27·3 (17·7)	25·6 (16·4)	25·7 (16·5)

Data are mean (SD) or n (%). ETDRS=Early Treatment Diabetic Retinopathy Study. LLD=low-luminance deficit. NL-BCVA=normal-luminance best-corrected visual acuity. *Some countries do not allow the collection of data on race and ethnicity; thus, a Not reported category was added to account for this aspect. †Drusen and LLD are often reported as baseline clinical characteristics of patients with geographic atrophy, but are not further discussed in this Article, as further analyses of these factors are not reported here. ‡The approximate Snellen chart equivalent values for baseline visual acuity were from 20/60 to 20/70. §In OAKS and DERBY, LLD at baseline was available for 201 patients and 199 patients in the pegcetacoplan monthly group, 204 patients and 199 patients in the pegcetacoplan every-other-month group, and 207 patients and 192 patients in the sham group, respectively.

Table 1: Demographic and baseline characteristics of the modified intention-to-treat population at 24 months

Role of the funding source

The funder conceived and designed the studies, and was responsible for site monitoring, data collection from investigators, and data analysis. The authors interpreted the data and wrote the manuscript with independent medical writing assistance, supported by the funder.

Results

Between Aug 30, 2018, and July 3, 2020, 1325 patients were screened in the OAKS trial and 1336 in the DERBY trial, of whom 688 in OAKS and 715 in DERBY were excluded (figure 1). The three most common reasons for exclusion were not meeting the lesion size eligibility criteria, not willing and able to provide informed consent and to comply with study procedures and assessments, and history of active CNV associated with AMD or other cause in the study eye. 637 patients in OAKS and 621 patients in DERBY were randomly assigned to the four treatment groups. 565 (89%) patients in OAKS and 550 (89%) patients in DERBY

completed the first 12 months of the study, and 471 (74%) patients in OAKS and 469 (76%) patients in DERBY completed 24 months (figure 1). The modified intention-to-treat populations of the OAKS and DERBY trials comprised 614 (96%) patients and 597 (96%) patients, respectively. Mean study drug compliance at month 12 was higher than 89% in both trials and higher than 87% at month 24 (appendix 1 p 17). The demographic and baseline characteristics of the modified intention-to-treat population were generally well balanced across the pegcetacoplan and sham groups in OAKS and DERBY (table 1).

In OAKS, the primary endpoint at 12 months was met, with pegcetacoplan monthly showing a significant –21% difference in total area of geographic atrophy lesion growth compared with sham (absolute difference in least-squares mean -0.41 mm^2 , -0.64 to -0.18 ; $p=0.0004$); a significant –16% difference in total area of geographic atrophy lesion growth was also observed with pegcetacoplan every other month (-0.32 mm^2 , -0.54 to

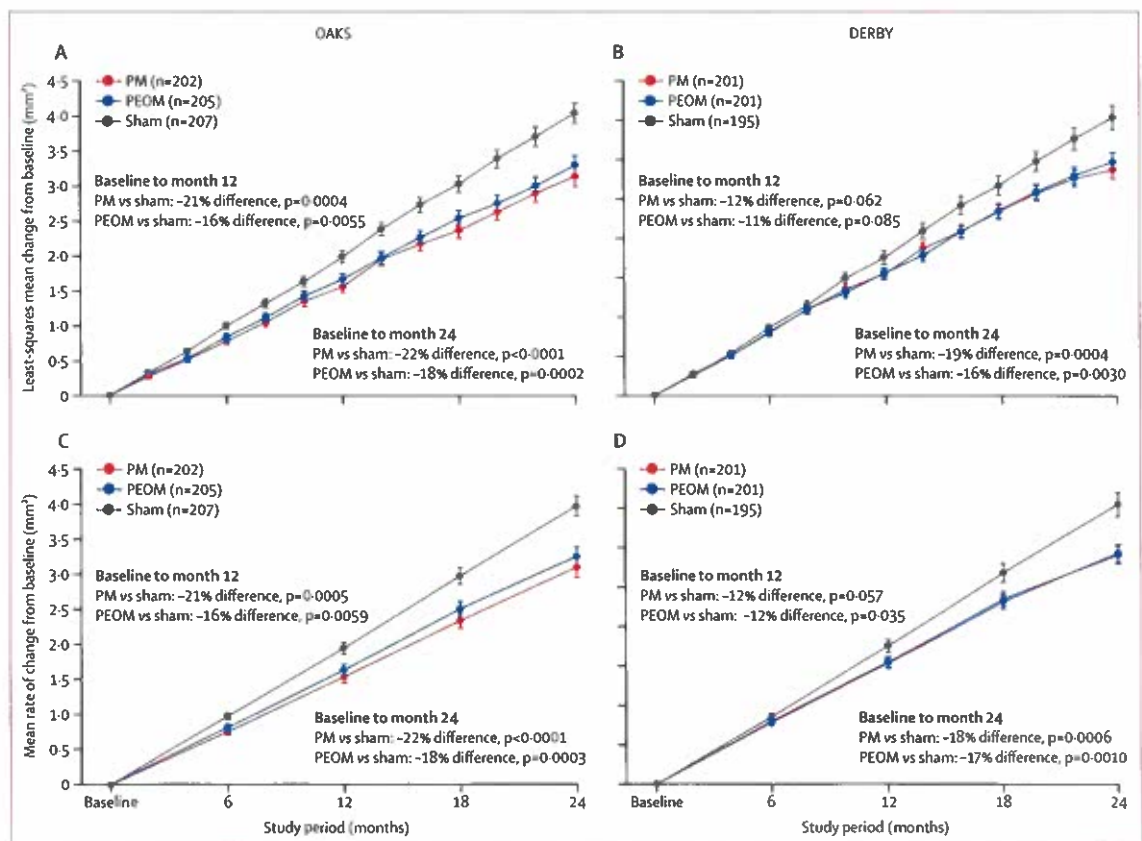


Figure 2: Least-squares mean change in geographic atrophy lesion area in OAKS and DERBY

Least-squares mean change in the total area of geographic atrophy lesions from baseline to month 24 in OAKS (A) and DERBY (B). Mean rate of change in the total area of geographic atrophy lesions from baseline to month 24 in OAKS (C) and DERBY (D), assuming a piecewise linear trend in time with a knot every 6 months, which allowed for the slope to be linear during each of the 6-month segments but to differ between segments. Error bars show SEs. For (A), 202, 204, and 206 patients were included in the OAKS MMRM analysis model for the PM, PEOM, and sham groups, respectively. For (B), 200, 200, and 194 patients were included in the DERBY MMRM analysis model for the PM, PEOM, and sham groups, respectively. MMRM=mixed-effect model for repeated measures. PEOM=pegcetacoplan every other month. PM=pegcetacoplan monthly.

–0.09; $p=0.0055$; figure 2A, table 2) compared with sham. At 24 months, pegcetacoplan monthly and pegcetacoplan every other month slowed the growth of geographic atrophy lesions by 22% (-0.90 mm^2 , -1.30 to -0.50 ; $p<0.0001$ [nominal]) and 18% (-0.74 mm^2 , -1.13 to -0.36 ; $p=0.0002$ [nominal]) compared with sham, respectively (figure 2A, table 2). In DERBY, the 12-month primary endpoint was not met; the growth differences of -12% (-0.23 mm^2 , -0.47 to 0.01 ; $p=0.062$) with pegcetacoplan monthly and -11% (-0.21 mm^2 , -0.44 to 0.03 ; $p=0.085$) with pegcetacoplan every other month compared with sham were not significant (figure 2B, table 2). At 24 months, pegcetacoplan monthly and pegcetacoplan every other month slowed the growth of geographic atrophy by 19% (-0.75 mm^2 , -1.15 to -0.34 ; $p=0.0004$ [nominal]) and 16% (-0.63 mm^2 , -1.05 to -0.22 ; $p=0.0030$ [nominal]) compared with sham, respectively (figure 2B, table 2). Observed data on lesion size and growth at months 6, 12, 18, and 24 are reported in appendix 1 (pp 18–19).

Preplanned sensitivity analyses indicated that the results of the mixed-effect model for repeated measures at month 12 (data not shown) and month 24 were robust to missing data, regardless of reason as well as other model assumptions (appendix 1 pp 20–21).

Findings from the post-hoc piecewise linear slope model were consistent with those of the prespecified mixed-effect model for repeated measures (figure 2C–D). In OAKS, at 12 months, pegcetacoplan monthly and pegcetacoplan every other month slowed the rate of geographic atrophy lesion growth by 21% (-0.41 mm^2 , -0.64 to -0.18 ; $p=0.0005$ [nominal]) and 16% (-0.31 mm^2 , -0.54 to -0.09 ; $p=0.0059$ [nominal]) compared with sham, respectively (figure 2C). In DERBY, at 12 months, pegcetacoplan monthly and pegcetacoplan every other month slowed the rate of geographic atrophy lesion growth by 12% (-0.23 mm^2 , -0.46 to 0.01 ; $p=0.057$ [nominal]) and 12% (-0.25 mm^2 , -0.46 to -0.02 ; $p=0.035$ [nominal]) compared with sham, respectively (figure 2D).

In the combined studies, the growth difference in geographic atrophy lesions at 12 months was -16% (-0.32 mm², -0.49 to -0.16; $p=0.0001$ [nominal]) with pegcetacoplan monthly and -14% (-0.27 mm², -0.43 to -0.10; $p=0.0014$ [nominal]) with pegcetacoplan every other month compared with sham (figure 3A). The growth difference in geographic atrophy lesions at 24 months was -21% (-0.82 mm², -1.11 to -0.54; $p<0.0001$ [nominal]) with pegcetacoplan monthly and -17% (-0.69 mm², -0.97 to -0.40; $p<0.0001$ [nominal]) with pegcetacoplan every other month compared with sham (figure 3A). A post-hoc piecewise linear slope analysis showed increasing efficacy of pegcetacoplan over time, with -30% difference with pegcetacoplan monthly and -24% difference with pegcetacoplan every other month in the growth rate of geographic atrophy lesions compared with sham, during months 18–24 (figure 3B). In the combined studies, the

	Month 12				Month 24											
	OAKS				DERBY				OAKS				DERBY			
	Pegcetacoplan monthly (n=202)	Pegcetacoplan every other month (n=205)	Sham (n=207)	Pegcetacoplan monthly (n=201)	Pegcetacoplan every other month (n=201)	Sham (n=195)	Pegcetacoplan monthly (n=202)	Pegcetacoplan every other month (n=205)	Sham (n=207)	Pegcetacoplan monthly (n=201)	Pegcetacoplan every other month (n=201)	Sham (n=195)				
Patients included in the model*	202 (100%)	204 (>99%)	205 (99%)	200 (>99%)	199 (99%)	193 (99%)	202 (100%)	204 (>99%)	206 (>99%)	200 (>99%)	200 (>99%)	194 (99%)				
Least-squares mean change (SE) from baseline, mm ³	1.56 (0.08)	1.65 (0.08)	1.97 (0.08)	1.73 (0.08)	1.76 (0.07)	1.96 (0.10)	3.12 (0.14)	3.28 (0.13)	4.03 (0.15)	3.23 (0.13)	3.34 (0.13)	3.97 (0.17)				
Absolute difference (95% CI) in least-squares mean pegcetacoplan vs sham, mm ³ (ie, primary outcome)	-0.41 (-0.64 to -0.18)	-0.32 (-0.54 to -0.09)	NA	-0.23 (-0.47 to 0.01)	-0.21 (-0.44 to 0.03)	NA	-0.90 (-1.30 to -0.50)	-0.74 (-1.13 to -0.36)	NA	-0.75 (-1.15 to -0.34)	-0.63 (-1.05 to -0.22)	NA				
Percentage difference pegcetacoplan vs sham	-21%	-16%	NA	-12%	-11%	NA	-22%	-18%	NA	-19%	-16%	NA				
p value pegcetacoplan vs sham	0.0004	0.0055	NA	0.062	0.085	NA	<0.0001	0.0002	NA	0.0004	0.0030	NA				
Data are n (%), unless otherwise stated. NA=not applicable. *Detailed information of the model is given in appendix 1 (p 10).																

Table 2: Least-squares mean change in the total area of geographic atrophy lesions from baseline to month 12 and month 24

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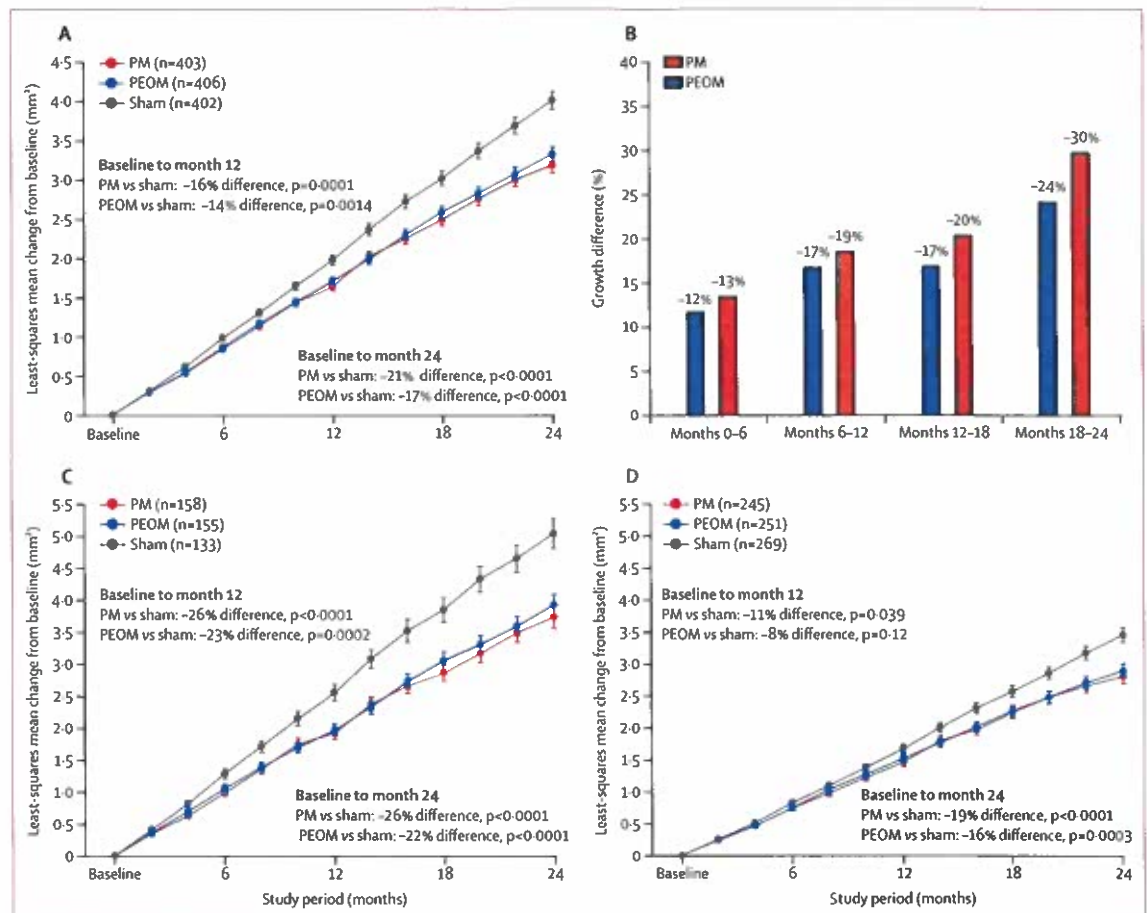


Figure 3: Least-squares mean change in geographic atrophy lesion area in OAKS and DERBY combined

Least-squares mean change in the total area of geographic atrophy lesions from baseline to month 24 in OAKS and DERBY combined (A). Percentage difference in growth of geographic atrophy lesions from baseline to month 24 in OAKS and DERBY combined compared with sham, assuming a piecewise linear trend in time with a knot every 6 months (B). Total area of non-subfoveal (C) and subfoveal (D) geographic atrophy lesions from baseline to month 24 in OAKS and DERBY combined. Error bars show SEs. For (A), 402, 404, and 400 patients were included in the MMRM analysis for the PM, PEOM, and sham groups, respectively. For (C), 158, 154, and 131 patients were included in the MMRM analysis for the PM, PEOM, and sham groups, respectively. For (D), 244, 250, and 269 patients were included in the MMRM analysis for the PM, PEOM, and sham groups, respectively. MMRM=mixed-effect model for repeated measures. PEOM=pegcetacoplan every other month. PM=pegcetacoplan monthly.

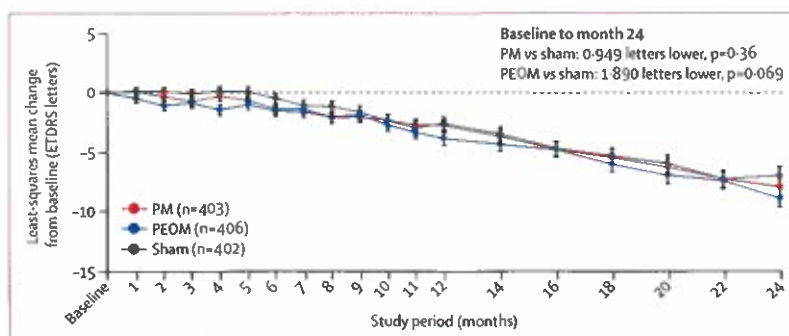


Figure 4: Least-squares mean change in normal-luminance best-corrected visual acuity score in the study eye of participants of OAKS and DERBY combined
Change from baseline to month 24 was measured on ETDRS charts. Error bars show SEs. ETDRS=Early Treatment Diabetic Retinopathy Study. PEOM=pegcetacoplan every other month. PM=pegcetacoplan monthly.

p values associated with the linear trend test were 0.0089 for pegcetacoplan monthly and 0.028 for pegcetacoplan every other month, indicating a trend for increasing treatment effects over time.

Foveal involvement is a key predictor of geographic atrophy lesion growth;² we thus did a prespecified subgroup analysis of the change in lesion size by lesion location (non-subfoveal, figure 3C vs subfoveal, figure 3D) from baseline to month 24 in OAKS and DERBY combined. Differences in lesion growth at month 12 were -26% (-0.66 mm^2 , -0.98 to -0.35; $p<0.0001$ [nominal]) and -23% (-0.59 mm^2 , -0.89 to -0.28; $p=0.0002$ [nominal]) in patients with non-subfoveal geographic atrophy lesions in the pegcetacoplan monthly and pegcetacoplan every-other-month groups, respectively, compared with sham. For patients with subfoveal lesions, differences in lesion

growth at month 12 were -11% (-0.19 mm^2 , -0.37 to -0.01 ; $p=0.039$ [nominal]) in patients in the pegcetacoplan monthly group and -8% (-0.66 mm^2 , -0.98 to -0.35 ; $p=0.12$ [nominal]) in those in the pegcetacoplan every-other-month group, compared with sham.

At 24 months, differences between treatment groups and sham in visual function endpoints of best-corrected visual acuity, functional reading independence index scores, monocular maximum reading speed, mean threshold sensitivity as assessed by mesopic microperimetry, and NEI VFQ-25 distance activity subscale score were not significant (figure 4, table 3). Compared with sham, the difference in the mean change in the number of scotomatous points in the junctional zone was not significant with pegcetacoplan monthly ($p=0.14$) and significant with pegcetacoplan every other month (0.014 ; appendix 1 p 22).

TEAEs at months 12 and 24 are summarised in table 4. In OAKS and in DERBY, the number of serious ocular TEAEs in the study eye was low (with TEAEs reported in five [2%] of 213, four [2%] of 212, and one [$<1\%$] of 211 patients in OAKS, and in four [2%] of 206, two [1%] of 208, and two [1%] of 206 patients in DERBY receiving pegcetacoplan monthly, pegcetacoplan every other month, and sham, respectively, at 24 months; appendix 1 pp 23–24). In OAKS and DERBY combined, the rates of intraocular inflammation were 0.22% per injection at 12 months (observed in 13 patients [14 events] treated with pegcetacoplan) and 0.24% per injection at 24 months (observed in 25 patients [28 events] treated with pegcetacoplan). After study initiation, four cases of intraocular inflammation (including one case of non-infectious endophthalmitis) were observed and linked to drug impurity, and the studies were placed on voluntary hold by the sponsor in October, 2018. The drug impurity

	Pegcetacoplan monthly	Pegcetacoplan every other month	Sham
Monocular maximum reading speed			
Patients included in the model*	347/403 (86%)	344/406 (85%)	345/402 (86%)
Least-squares mean change (SE), words per min†	-22.49 (2.57)	-21.35 (2.16)	-19.13 (2.40)
Difference (95% CI) in least-squares mean pegcetacoplan vs sham, words per min	-3.36 (-9.89 to 3.17)	-2.23 (-8.20 to 3.75)	NA
p value pegcetacoplan vs sham	0.31	0.47	NA
Functional reading independence index score			
Patients included in the model‡	371/403 (92%)	376/406 (93%)	373/402 (93%)
Least-squares mean change (SE), score	-0.35 (0.04)	-0.37 (0.04)	-0.32 (0.04)
Difference (95% CI) in least-squares mean pegcetacoplan vs sham, score	-0.03 (-0.14 to 0.08)	-0.06 (-0.16 to 0.05)	NA
p value pegcetacoplan vs sham	0.58	0.30	NA
Normal-luminance best-corrected visual acuity score			
Patients included in the model§	403/403 (100%)	406/406 (100%)	402/402 (100%)
Least-squares mean change (SE), ETDRS letters	-7.89 (0.74)	-8.83 (0.74)	-6.94 (0.74)
Difference (95% CI) in least-squares mean pegcetacoplan vs sham, ETDRS letters	-0.95 (-2.97 to 1.07)	-1.89 (-3.93 to 0.15)	NA
p value pegcetacoplan vs sham	0.36	0.069	NA
National Eye Institute Visual Functioning Questionnaire 25 distance activity subscale score			
Patients included in the model¶	375/403 (93%)	380/406 (94%)	377/402 (94%)
Least-squares mean change (SE), score	-10.98 (1.35)	-10.10 (1.26)	-9.93 (1.19)
Difference (95% CI) in least-squares mean pegcetacoplan vs sham, score	-1.05 (-4.35 to 2.25)	-0.17 (-3.35 to 3.00)	NA
p value pegcetacoplan vs sham	0.53	0.92	NA
Mean threshold macular sensitivity			
Patients included in the model	179/202 (89%)	187/205 (91%)	186/207 (90%)
Least-squares mean change (SE), decibel	-3.32 (0.30)	-3.06 (0.23)	-2.95 (0.22)
Difference (95% CI) in least-squares mean pegcetacoplan vs sham, decibel	-0.37 (-1.06 to 0.33)	-0.11 (-0.69 to 0.47)	NA
p value pegcetacoplan vs sham	0.30	0.71	NA
Data are n/N (%), unless otherwise stated. Secondary endpoints were analysed in OAKS and DERBY combined, except for the macular sensitivity measurement, which was only evaluated in OAKS. ETDRS=Early Treatment Diabetic Retinopathy Study. NA=not applicable. *Detailed information of the model is given in appendix 1 (p 11). †Maximum reading speed was calculated as the mean of the three highest non-zero reading speeds (or two, or one value, as available), except when all three reading speed values were 0, in which case the maximum reading speed was set at 0. ‡Detailed information of the model is given in appendix 1 (p 11). §Detailed information of the model is given in appendix 1 (p 11). ¶Detailed information of the model is given in appendix 1 (p 11). Detailed information of the model is given in appendix 1 (p 11).			

Table 3: Visual function endpoint results from baseline to month 24

was removed, and the studies resumed in March, 2019. No cases of retinitis or vasculitis (occlusive or non-occlusive) were reported during the whole study. Of 26 patients treated with pegcetacoplan and sham with intraocular inflammation at 24 months, 17 (65%) reported adverse events as mild, three (12%) as moderate, and six (23%) as severe. Two of the severe events were included in the four events attributed to drug impurity in 2018. By the end of the study, the majority of patients who had intraocular inflammation during the study recovered their vision to the value they had before intraocular inflammation; two patients had loss of 15 letters or more at the last observed value. No event of intraocular inflammation led to permanent, severe vision loss (≥ 30 letters lost), and most patients (20 [77%] of 26) resumed treatment without subsequent recurrence of intraocular inflammation. No events of intraocular inflammation were reported to have retinal involvement.

Four cases of infectious endophthalmitis were reported in 24 months. For OAKS and DERBY combined, the rates of infectious endophthalmitis were 0.05% per injection at 12 months (observed in three patients [three events] treated with pegcetacoplan) and 0.03% per injection at 24 months (observed in four patients [four events] treated with pegcetacoplan). When the infectious endophthalmitis events were considered resolved, visual acuity had recovered to levels consistent

with baseline values (within five letters) for all patients. Three serious adverse events of ischaemic optic neuropathy were reported in three patients receiving pegcetacoplan monthly over 24 months (appendix 1 p 23). The most common ocular TEAEs in the study eyes are reported in appendix 1 (p 25).

Fellow-eye CNV at baseline—an important risk factor for the development of exudative AMD in the study eye²²—was identified in 45 (21%), 39 (18%), and 45 (21%) patients in OAKS, and in 39 (19%), 42 (20%), and 42 (20%) patients in DERBY who received pegcetacoplan monthly, pegcetacoplan every other month, and sham, respectively (appendix 1 p 26). At 12 months, investigator-determined events of new-onset exudative AMD were reported in 11 (5%; 11 events), ten (5%; ten events), and three (1%; three events) patients in OAKS, and in 14 (7%; 15 events), seven (3%; seven events), and seven (3%; eight events) patients in DERBY with pegcetacoplan monthly, pegcetacoplan every other month, and sham, respectively. New-onset exudative AMD was reported in 24 (11%; 25 events), 16 (8%; 17 events), and four (2%; four events) patients in OAKS, and in 27 (13%; 30 events), 12 (6%; 12 events), and nine (4%; 11 events) patients in DERBY receiving pegcetacoplan monthly, pegcetacoplan every other month, and sham, respectively, at 24 months (table 2).

On gradable fluorescein angiography images taken at the study visit at which new-onset exudative AMD was

	OAKS						DERBY					
	Pegcetacoplan monthly (n=213)		Pegcetacoplan every other month (n=212)*		Sham (n=211)		Pegcetacoplan monthly (n=206)		Pegcetacoplan every other month (n=208)		Sham (n=206)	
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events
All TEAEs												
Month 12	171 (80%)	757	161 (76%)	740	155 (73%)	702	159 (77%)	723	157 (75%)	612	145 (70%)	547
Month 24 (cumulative)	192 (90%)	1368	187 (88%)	1201	175 (83%)	1148	178 (86%)	1215	180 (87%)	1019	169 (82%)	936
Ocular TEAEs in the study eye												
Month 12	108 (51%)	257	97 (46%)	210	74 (35%)	158	102 (50%)	230	92 (44%)	165	73 (35%)	127
Month 24 (cumulative)	133 (62%)	399	123 (58%)	313	98 (46%)	236	125 (61%)	354	108 (52%)	258	95 (46%)	184
Non-ocular TEAEs												
Month 12	137 (64%)	398	128 (60%)	428	126 (60%)	448	129 (63%)	403	112 (54%)	346	113 (55%)	342
Month 24 (cumulative)	174 (82%)	787	165 (78%)	729	154 (73%)	742	163 (79%)	719	142 (68%)	613	146 (71%)	629
Patients with investigator-determined new-onset exudative AMD in the study eye†												
Month 12	11 (5%)	11	10 (5%)	10	3 (1%)	3	14 (7%)	15	7 (3%)	7	7 (3%)	8
Month 24 (cumulative)	24 (11%)	25	16 (8%)	17	4 (2%)	4	27 (13%)	30	12 (6%)	12	9 (4%)	11
Patients with intraocular inflammation in the study eye‡§												
Month 12	7 (3%)	7	2 (1%)	2	0	0	2 (1%)	3	2 (1%)	2	0	0
Month 24 (cumulative)	11 (5%)	11	3 (1%)	3	1 (0%)	1	5 (2%)	6	6 (3%)	8	0	0
Patients with infectious endophthalmitis in the study eye												
Month 12	1 (0%)	1	2 (1%)	2	0	0	0	0	0	0	0	0
Month 24 (cumulative)	2 (1%)	2	2 (1%)	2	0	0	0	0	0	0	0	0

Data are n (%) or n. AMD=age-related macular degeneration. TEAE=treatment-emergent adverse event. *One patient was not at risk for new exudative AMD because they had a previous history of choroidal neovascularisation. †Exudative AMD events include Medical Dictionary for Regulatory Activities preferred terms of choroidal neovascularisation and neovascular AMD. ‡To measure the per-injection risk of inflammation and prevent double counting a patient, multiple TEAEs on the same day were counted as a single TEAE and multiple TEAEs on different days were counted as separate TEAEs. §The four events of intraocular inflammation linked to drug impurity are included here, including one event of non-infectious endophthalmitis.

Table 4: Overall safety data from baseline to month 12 and month 24 in the safety population

diagnosed, 14 (78%), 14 (100%), and three (100%) patients in OAKS, and 14 (82%), seven (78%), and eight (89%) patients in DERBY who received pegcetacoplan monthly, pegcetacoplan every other month, and sham, respectively, had occult CNV (appendix 1 p 27). Patients who developed exudative AMD continued study treatment and most of them received anti-VEGF therapy in accordance with the study protocol (50 [98%] of 51 patients receiving pegcetacoplan monthly, 27 [96%] of 28 patients receiving pegcetacoplan every other month, and 11 [85%] of 13 patients receiving sham). Mean anti-VEGF injection frequency was approximately one injection every other month. No patient treated with pegcetacoplan who developed exudative AMD discontinued the study due to exudative AMD. No case of exudative AMD was reported as a serious adverse event; one exudative AMD event in a patient treated with pegcetacoplan led to pegcetacoplan discontinuation, but not study discontinuation. Median change in best-corrected visual acuity from the study visit preceding exudative AMD to the visit at month 24 was -5.0 letters (IQR -14.0 to 0.0) in patients receiving pegcetacoplan monthly, -6.0 letters (-11.0 to -1.0) in those receiving pegcetacoplan every other month, and -5.0 letters (-12.0 to 2.0) in those receiving sham, measured during a median follow-up period of 447 days (238 to 613). When pegcetacoplan was co-administered with anti-VEGF treatment, no unexpected outcomes were observed.

Discussion

Pegcetacoplan slowed geographic atrophy lesion growth in the OAKS and DERBY studies compared with sham, with increasing effects over time in both patients receiving pegcetacoplan monthly and those receiving pegcetacoplan every other month in the combined studies. To our knowledge, OAKS is the first phase 3 study of patients with geographic atrophy to meet its primary endpoint with a statistically significant growth difference in geographic atrophy lesions at 12 months in patients receiving pegcetacoplan monthly and pegcetacoplan every other month compared with sham. DERBY did not meet the primary endpoint at 12 months, potentially due to imbalances in disease characteristics. Considering the established link between geographic atrophy (which appears hypofluorescent on FAF images) and retinal pigment epithelium cell death and photoreceptor loss,⁷ and considering the slowing of the rate of change of lesion growth shown in the piecewise linear slope analysis, pegcetacoplan slowed the progression of geographic atrophy and potentially preserved photoreceptor function; however, further research is needed to better elucidate this aspect.

Previous studies targeting the alternative complement pathway did not slow geographic atrophy progression;^{8,23} however, C3 is a promising target because complement activation via any pathway leads to the cleavage of C3, resulting in amplification of the complement response.^{10,21}

Overactivation of the complement system might increase opsonisation and phagocytosis of photoreceptor outer segments.²⁴ Pegcetacoplan binds C3 and prevents its cleavage, suppressing the downstream effects of excessive complement activation.¹³ These results provide evidence that excessive complement activation could contribute to geographic atrophy progression. In post-hoc analyses of images from the FILLY study, pegcetacoplan treatment slowed degeneration of photoreceptors and retinal pigment epithelium outside areas of geographic atrophy.^{11,25,26}

Studies investigating the topographical density of photoreceptors have shown that cone density of the average eye reaches a peak of approximately 200 000 cones per mm² at the centre zone and decreases with eccentricity.²⁷ Therefore, preservation of 1.0 mm² of the central macula retinal tissue could equate to preservation of up to 200 000 cone cells.²⁷ Considering that the size of the fovea is approximately 1.75 mm², the average magnitude of retinal preservation observed with pegcetacoplan treatment (0.2–0.4 mm² during a 12-month period; 0.6–0.9 mm² during a 24-month period) might be biologically meaningful. The results of the combined analyses indicate that the effects increase over time.

With the effects of pegcetacoplan on geographic atrophy lesion growth observed at 24 months, improvements were observed on microperimetry for scotomatous points within the junctional zone of geographic atrophy in patients receiving pegcetacoplan. However, no significant differences were observed for other visual function measures. OAKS and DERBY included the most suitable functional measures currently available for clinical trials, but unlike the objective, anatomical, primary endpoint, which has high spatial resolution, functional measures are subjective, have high variability, and can be confounded by shifts in location of the preferred retinal locus;^{18,29} moreover, these measures (including microperimetry, with a relatively sparse grid) have low spatial resolution and therefore are not optimal measures of visual function deterioration in patients with geographic atrophy.

Of all the functional endpoints, scotomatous points have the strongest correlation with anatomical measures, whereas other functional endpoints exhibit weak correlations.¹⁸ These weak correlations are attributed to both the heterogeneous clinical presentation of geographic atrophy, in which lesion size, location, and growth rate can vary substantially, and the fact that the functional endpoints were not originally designed specifically to capture changes in vision in patients with geographic atrophy. When limiting microperimetry analysis to points within the area at greatest risk for functional loss due to progressive atrophy (ie, at the junctional zone), reductions in the number of new scotomatous points were seen with pegcetacoplan (non-significant with pegcetacoplan monthly and significant with pegcetacoplan every other

month) compared with sham. Although this finding might indicate functional benefit in an area with an observed anatomical benefit, given the post-hoc nature of this analysis, further studies are needed to substantiate this finding.

The safety profile of pegcetacoplan was generally similar to that observed in other studies of intravitreal agents, with the exception of the observation of new-onset exudative AMD.^{13,23,30} In OAKS and DERBY, new-onset exudative AMD incidence was higher in patients treated with pegcetacoplan than in those receiving sham, as previously reported in FILLY; however, incidence of exudative AMD was lower in patients receiving pegcetacoplan in OAKS and DERBY than in patients receiving pegcetacoplan in FILLY.²²

Potential limitations of the studies include the high proportion of patients with subfoveal geographic atrophy, which might have made the assessment of the effects on visual function more challenging. Optical coherence tomography angiography imaging was not available at all sites, preventing a systematic evaluation of the presence of non-exudative neovascularisation at baseline. Study-mandated imaging provided information on neovascularisation subtype for patients who developed new-onset exudative AMD in the study eye, but this information was not collected for any CNV that might have existed in the fellow eye at the time of enrolment. A potential source of bias could be missing data due to study discontinuations; preplanned sensitivity analyses suggest the effect of pegcetacoplan monthly and pegcetacoplan every other month on lesion growth indicate that the results at 12 months and 24 months were robust to missing data, but the potential impact of the COVID-19 pandemic cannot be quantified with certainty.

Therapeutic options for patients with geographic atrophy are a crucial unmet need. With the approval of pegcetacoplan by the FDA for the treatment of geographic atrophy secondary to AMD, a recognition of the clinical meaningfulness of slowing the rate of lesion growth, a much-needed therapeutic option has become available to patients. Pegcetacoplan slowed the growth of total area of geographic atrophy lesions, with increasing effects over time compared with sham. Pegcetacoplan was well tolerated in two phase 3 studies following up more than 1200 patients for 2 years, with nearly 12000 injections administered, which support its use as a treatment option for geographic atrophy. To our knowledge, these results are the first phase 3 data to support the complement system as an appropriate target in the treatment of geographic atrophy.

The long-term efficacy and safety of pegcetacoplan will be investigated in GALE, a 3-year, open-label, extension study (NCT04770545).

Contributors

All authors reviewed and interpreted the data, critically reviewed the manuscript, and provided comments that were incorporated. All authors

had input into the figures and tables. CCW and CB directly accessed and verified the underlying data reported in this manuscript. All authors had full access to study data and had final responsibility for the decision to submit for publication.

Declaration of interests

JSH has received grants paid to their institution from Annexon Biosciences, Apellis Pharmaceuticals, AsclepiX Therapeutics, Bayer, Genentech/Roche, Gyroscope Therapeutics, Iveric Bio, iCyt, Kodiak Sciences, NGM Biopharmaceuticals, Notal Vision, Regeneron Pharmaceuticals, and Regenxbio; and consultancy fees from 4DMT, Adverum Biotechnologies, AffaMed, Allegro Ophthalmics, Allergan, Annexon Biosciences, Apellis Pharmaceuticals, AsclepiX Therapeutics, Genentech/Roche, Gyroscope Therapeutics, Iveric, Janssen R&D, Chengdu Kanghong Pharmaceutical Group, NGM Biopharmaceuticals, Novartis, OcuTerra, Regenxbio, Regeneron Pharmaceuticals, RevOpsis, Stealth BioTherapeutics, and Thea Laboratories. EML has received grants paid to their institution from Boehringer Ingelheim; research funding from Alexion Pharmaceuticals, Apellis Pharmaceuticals, Astellas Pharma, Boehringer Ingelheim, Gemini Therapeutics, Janssen, LumiThera, Neurotech, Novartis, and Roche; and consultancy fees from Alexion Pharmaceuticals, Allegro Ophthalmics, Annexon Biosciences, Apellis Pharmaceuticals, EdiGeneBio, Galimedix Therapeutics, Gemini Therapeutics, Iveric Bio, Janssen, LumiThera, Nanoscope Therapeutics, NGM Biopharmaceuticals, Novartis, Perceive Biotherapeutics, Retrotape, Roche, and Thea Laboratories; holds a provisional patent (A System and Method to Predict Progression of Age-Related Macular Degeneration; US patent application number 63162741); holds stock options with Retrotape; and is the recipient of medical writing services from Allegro Ophthalmics, Apellis Pharmaceuticals, and Boehringer Ingelheim. FGH has received grants paid to their institution and consultancy fees from Apellis Pharmaceuticals, Iveric Bio, Genentech/Roche, Pixium Vision, and Heidelberg Engineering; financial support from Apellis Pharmaceuticals, Genentech/Roche, and Heidelberg Engineering; is an executive board member of EURETINA and the German Ophthalmological Society; and is a scientific board member of Pro Retina. PJR has stock options in Apellis Pharmaceuticals. RHG has received consultancy fees from Apellis Pharmaceuticals, Bayer, Genentech/Roche, and Novartis; and financial support from Apellis Pharmaceuticals and Genentech/Roche. DB has received consultancy fees from Alexion Pharmaceuticals, Annexon Biosciences, Apellis Pharmaceuticals, Boehringer Ingelheim, Cell Cure Neurosciences, Gemini Therapeutics, Genentech, Gyroscope Therapeutics, Ionis Pharmaceuticals, Iveric Bio, and Stealth BioTherapeutics; holds stock in Digsight and Ora; and is an equity owner in Apellis Pharmaceuticals. FG is a patent inventor (US patent application number 15/766,795 [Dosing Regimens] and Patent Cooperation Treaty [PCT] application number PCT/US2022/043127 [Treatment of Geographic Atrophy]); the patent rights are assigned to Apellis Pharmaceuticals; is an equity owner in Apellis Pharmaceuticals; and is an employee of Apellis Pharmaceuticals. CRB has received financial support from Apellis Pharmaceuticals; and is the Chief Medical Officer of Apellis Pharmaceuticals. J-FK has received consultancy fees from Apellis Pharmaceuticals, Bayer, Janssen, Nano Retina, Roche, Thea Laboratories, and Carl Zeiss Meditec; and is a member of a data safety monitoring board for Alexion Pharmaceuticals and Novo Nordisk. JSS has received a grant paid to their institution, consultancy fees, and financial support from Apellis Pharmaceuticals; and has stock in Apellis Pharmaceuticals. NKW has received a grant paid to their institution from Nidek, Topcon, and Zeiss; consulting fees from Complement Therapeutics, Hubble Therapeutics, Iolyx Therapeutics, OliX Pharmaceuticals, SalioGen Therapeutics, Syncona, and Topcon; financial support from Nidek; is an officeholder at AGTC; and has an equity interest in Gyroscope Therapeutics and OcuDyne. RM is an employee of Apellis Pharmaceuticals. IP has received consultancy fees from Apellis Pharmaceuticals, Bayer, Novartis, and Roche; and financial support from Apellis Pharmaceuticals, Bayer, and Novartis. NS has received consultancy fees from Apellis Pharmaceuticals, has received speaking honoraria from Apellis Pharmaceuticals, and has participated on a data safety monitoring board and advisory board for Apellis Pharmaceuticals. AAF has received a grant paid to their institution from Novartis and Roche; financial support from Allergan, Novartis, and Roche; holds a

patent for Probe for Identification of Ocular Tissues During Surgery (University of California Los Angeles reference number 2020-851-3 PCT); and holds stock in Apellis Pharmaceuticals and Iveric Bio. AH has received a grant paid to their institution and consultancy fees from Apellis Pharmaceuticals; and has stock in Apellis Pharmaceuticals. DRL has received a grant paid to their institution from Annexon Biosciences, Apellis Pharmaceuticals, Iveric Bio, and Stealth BioTherapeutics; consultancy fees from Annexon Biosciences, Apellis Pharmaceuticals, Applied Genetic Technologies Corporation, Iveric Bio, and Stealth BioTherapeutics; financial support from Annexon Biosciences, Apellis Pharmaceuticals, and Iveric Bio; is a steering committee member of Annexon Biosciences and Iveric Bio; and is a medical advisory board member of Applied Genetic Technologies Corporation. PD is an employee of Apellis Pharmaceuticals. PD and CF are inventors of several patents and authors of several patent applications covering pegcetacoplan or relating to methods of treating ophthalmologic indications (US patent numbers 8,168,584 [Methods of Treating Age-related Macular Degeneration by Compstatin and Analogs Thereof], 10,125,171 [Cell-reactive, Long-acting, or Targeted Compstatin Analogs and Uses Thereof], 10,035,822 [Cell-reactive, Long-acting, or Targeted Compstatin Analogs and Related Compositions and Methods]; US patent application number 15/766,795 [Dosing Regimens]; and PCT application number PCT/US2022/043127 [Treatment of Geographic Atrophy]; the patent rights are assigned to Apellis Pharmaceuticals). CF is an equity owner in Apellis Pharmaceuticals, and is an employee of Apellis Pharmaceuticals. CB has stock in Apellis Pharmaceuticals, and is an employee of Apellis Pharmaceuticals. GS has received grants for clinical trials from Apellis Pharmaceuticals, Genentech, and Iveric Bio; financial support from Apellis Pharmaceuticals; and has participated on a data safety monitoring board and advisory board for Apellis Pharmaceuticals, Bayer, Boehringer Ingelheim, Genentech, Iveric Bio, Novartis, and Roche. JM has been an investigator for Apellis Pharmaceuticals, Genentech, Ionis Pharmaceuticals, Iveric Bio, Kodiak Sciences, Novartis, ReNeuron, and Roche; has received consultancy fees from Annexon Biosciences, Apellis Pharmaceuticals, Cell Cure Neurosciences, EyeBio, Genentech, Iveric Bio, Lineage Cell Therapeutics, Maculogix, Novartis, and ReNeuron; financial support from Apellis Pharmaceuticals, Cell Cure Neurosciences, Genentech, Iveric Bio, Kodiak Sciences, Lineage Cell Therapeutics, Novartis, ReNeuron, and Roche; has participated on an advisory board for Apellis Pharmaceuticals, Cell Cure Neurosciences, Genentech, Iveric Bio, Kodiak Sciences, Lineage Cell Therapeutics, Novartis, ReNeuron, and Roche; and holds stock in Notal Vision. RPS has received consultancy fees from Alcon, Apellis Pharmaceuticals, AsclepiX Therapeutics, Bausch and Lomb, Genentech, Gyroscope Therapeutics, Novartis, and Regeneron Pharmaceuticals; financial support from Genentech, Novartis, and Regeneron Pharmaceuticals; is a member of the board of directors for the American Society of Retina Specialists; and is an executive board member of the Retina World Congress. RR is an equity owner in Apellis Pharmaceuticals, and an employee of Apellis Pharmaceuticals. CCW has received a grant paid to their institution from 4DMT, Adverum Biotechnologies, Aerie Pharmaceuticals, AffaMed, Aldeyra Therapeutics, Alexion Pharmaceuticals, Alimera Sciences, Alkermes, Allergan, Allgenesis, Amgen, Annexon Biosciences, Apellis Pharmaceuticals, AsclepiX Therapeutics, Bayer, Boehringer Ingelheim, Chengdu Kanghong Pharmaceutical Group, Clearside Biomedical, Curacle, EyePoint Pharmaceuticals, Gemini Therapeutics, Genentech, Graybug Vision, Gyroscope Therapeutics, Ionis Pharmaceuticals, iRenix, Iveric Bio, Kodiak Sciences, The Lowy Medical Research Institute, Nanoscope Therapeutics, Neurotech, NGM Biopharmaceuticals, Novartis, Ocular Therapeutix, Ocuphire Pharma, OcuTerra, Opthea, Oxular, Oxurion, Oyster Point Pharma, RecensMedical, Regeneron Pharmaceuticals, Regenxbio, Roche, SamChunDang Pharm, Sandoz, Taiwan Liposome, Unity Biotechnology, Verily, and Xbrane Biopharma; consultancy fees from 4DMT, AbbVie, Adverum Biotechnologies, Aerie Pharmaceuticals, AGTC, Alcon, Alimera Sciences, Allergan, Allgenesis, Alnylam Pharmaceuticals, Annexon Biosciences, Apellis Pharmaceuticals, Arrowhead Pharmaceuticals, Bausch and Lomb, Bayer, Bionic Vision Technologies, Boehringer Ingelheim, Chengdu Kanghong Pharmaceutical Group, Chologene Therapeutics, Clearside Biomedical, Curacle, EyePoint Pharmaceuticals, Foresite, Frontera Therapeutics,

Genentech, Gyroscope Therapeutics, IACTA Pharmaceuticals, Iveric Bio, Janssen, Kato Pharmaceuticals, Kiora Pharmaceuticals, Kodiak Sciences, Kriya Therapeutics, Merck, Nanoscope Therapeutics, NGM Biopharmaceuticals, Notal Vision, Novartis, OccuRx, Ocular Therapeutix, OcuTerra, OliX Pharmaceuticals, ONL Therapeutics, Opthea, Palatin Technologies, Perceive Biotherapeutics, Perfuse Therapeutics, PolyPhotonix, Ray Therapeutics, RecensMedical, Regeneron Pharmaceuticals, Regenxbio, Resonance Pharma, Roche, SciNeuro Pharmaceuticals, Stealth BioTherapeutics, Surrozen, Thea Laboratories, TissueGen, Valo Therapeutics, Verana Health, and Vitranu; has participated on a data safety monitoring board and advisory board for Aerie Pharmaceuticals and Kato Pharmaceuticals; is a board member of the American Society of Retina Specialists and the Vit-Buckle Society; and holds stock options in ONL Therapeutics, PolyPhotonix, RecensMedical, TissueGen, Visgenx, and Vitranu.

Data sharing

The data reported in this Article are available from the sponsor upon reasonable request. Individual participant data will not be made available. The study protocols are available in appendix 2. Requests for access to data from the OAKS and DERBY trials should be addressed to MedicalResearch@apellis.com. The study protocol will be available with no end date. All proposals requesting data access will need to specify how the data will be used, and all proposals will need the approval of the trial investigator team before data release.

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