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Efficacy and Safety of Intravitreal Pegcetacoplan in Geographic Atrophy: 24-Month Results From the Phase 3 OAKS and DERBY Trials

Ian Pearce, MBChB[1], Allen Chiang, MD[2], Sujata Sarda, PhD[3], Mark Burch, PhD[3], Min Tsuboi, PharmD[3], Daniel Jones, PhD[3], Ramiro Ribeiro, MD, PhD[3]

[1]Department of Ophthalmology, Royal Liverpool University Hospital, Liverpool, UK; [2]Wills Eye Hospital Retina Service, Philadelphia, PA, USA; [3]Apellis Pharmaceuticals, Inc., Waltham, MA, USA

Introduction

- Geographic atrophy (GA) pathogenesis encompasses a complex interaction of physiological, lifestyle/environmental, and genetic factors[1]
- The genes implicated in the pathogenesis of GA encode components of the complement system, and complement proteins have been shown to accumulate in drusen and the sub-retinal pigment epithelium space in age-related macular degeneration (AMD)[2,3]
- Pegcetacoplan is a complement inhibitor that binds C3 and C3b to control undesirable downstream effects from complement overactivation[4,5]

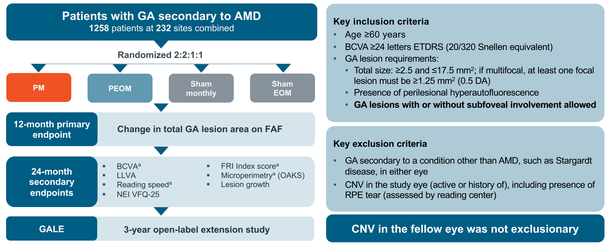
Purpose

- To study the efficacy and safety of pegcetacoplan in a broad heterogenous GA population in two 24-month, Phase 3 trials, OAKS and DERBY

Methods

- OAKS and DERBY enrolled 1258 patients according to the inclusion and exclusion criteria shown in **Figure 1**
- Patients were randomized (2:2:1:1) to receive intravitreal pegcetacoplan monthly (PM) or every other month (PEOM), or sham monthly or every other month (**Figure 1**)
- Here we report 24-month data from the trials, including the prespecified endpoints:
  - Reduction in GA lesion growth
  - Key functional outcomes, including best-corrected visual acuity (BCVA) and microperimetry (OAKS only)
- Junctional zone (area within 250 microns of each side of GA lesion border) was created on FAF for each patient (**Supplemental Figure 1; access via QR code**), and microperimetry endpoints were assessed within this region
- Efficacy of pegcetacoplan at 24 months was also assessed in patient subgroups per baseline demographics and GA lesion characteristics
  - Subgroups based on age, sex, GA lesion location, focality and laterality, and BCVA were analyzed

Figure 1. Trial Designs and Key Criteria



Key inclusion criteria
- Age ≥60 years
- BCVA ≥24 letters ETDRS (20/320 Snellen equivalent)
- GA lesion requirements:
  - Total size: ≥2.5 and ≤17.5 mm²; if multifocal, at least one focal lesion must be ≥1.25 mm² (0.5 DA)
  - Presence of perilesional hyperautofluorescence
  - **GA lesions with or without subfoveal involvement allowed**

Key exclusion criteria
- GA secondary to a condition other than AMD, such as Stargardt disease, in either eye
- CNV in the study eye (active or history of), including presence of RPE tear (assessed by reading center)

CNV in the fellow eye was not exclusionary

OAKS, DERBY, GALE CT.gov identifiers: NCT03525613, NCT03525600, NCT04770545, respectively.
[a]Key secondary endpoints.
AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; DA, disc area; EOM, every other month; ETDRS, Early Treatment Diabetic Retinopathy Study; FAF, fundus autofluorescence; FRI, Functional Reading Independence; GA, geographic atrophy; LLVA, low luminance visual acuity; NEI-VFQ, National Eye Institute Visual Function Questionnaire; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly; RPE, retinal pigment epithelium.

Results

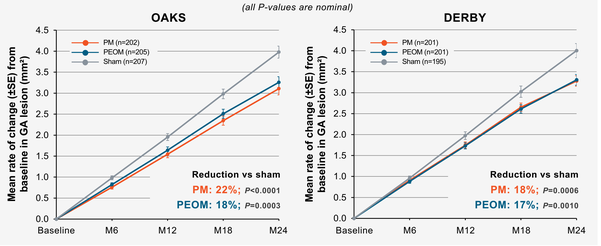
Patient Demographics and Baseline Characteristics

- Key demographics and baseline study eye characteristics of patients in OAKS (N=637) and DERBY (N=621) are shown in **Supplemental Table 1** (**access via QR code**)

Efficacy

- In a combined mixed-effects model for repeated measures (MMRM) analysis of OAKS and DERBY, pegcetacoplan reduced GA lesion growth versus sham by 21% PM and 17% PEOM (both *P*<0.0001) at 24 months (OAKS: 22% PM, *P*<0.0001; 18% PEOM, *P*=0.0002; DERBY: 19% PM, *P*=0.0004; 16% PEOM, *P*=0.0030; all *P*-values are nominal)
- In a post-hoc piecewise linear slope analysis, pegcetacoplan reduced GA lesion growth versus sham by 22% PM and 18% PEOM in OAKS and by 18% PM and 17% PEOM in DERBY at 24 months (**Figure 2**) (OAKS and DERBY combined: 20% PM; 17% PEOM, both *P*<0.0001)

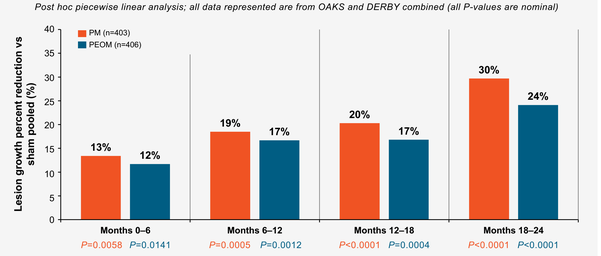
Figure 2. Reductions in GA Lesion Growth at Month 24 (Piecewise Linear Slope Analysis)



LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 24, with knots at Months 6, 12, and 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis). The modified intent-to-treat population was used for the analysis, defined as all randomized patients who received at least one injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.
GA, geographic atrophy; LS, least square; M, month; n, number of patients; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly; SE, standard error.

- In the combined studies, reductions in GA lesion growth versus sham for the 6-month period between 18 and 24 months was 30% and 24% (both *P*<0.0001) for PM and PEOM, respectively (**Figure 3**)

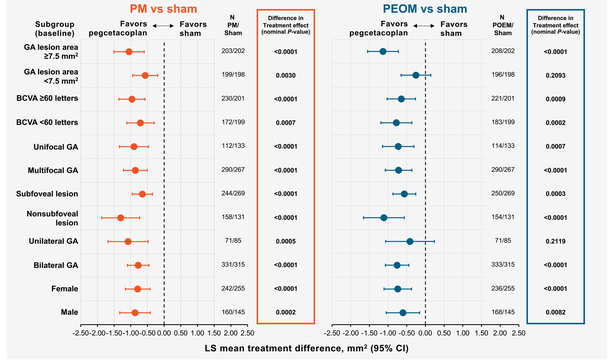
Figure 3. OAKS and DERBY Combined: Reductions in GA Lesion Growth by 6-Month Periods



Percent reduction vs sham pooled for Month 0 to Month 24 was estimated from a piecewise linear slope model with 6-month segments using the combined patient-level data, not a simple average of results, from the two studies. Point estimates for the Month 0 to Month 18 segments vary marginally from previously reported numbers owing to the inclusion of the Month 20 to Month 24 data into the statistical model.
GA, geographic atrophy; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly.

- In a combined MMRM analysis, reductions in GA lesion growth occurred in patients with both nonsubfoveal (26% PM; 22% PEOM, both *P*<0.0001) and subfoveal (19% PM, *P*<0.0001; 16% PEOM *P*=0.0003) lesions (**Supplemental Figure 2; access via QR code**)
- In the combined studies, change from baseline in GA lesion growth at Month 24 consistently favored pegcetacoplan versus sham across subgroups, including those with unifocal and multifocal lesions (**Figure 4**)

Figure 4. OAKS and DERBY Combined: Treatment Effect on GA Lesion Growth by Baseline Subgroup Characteristics

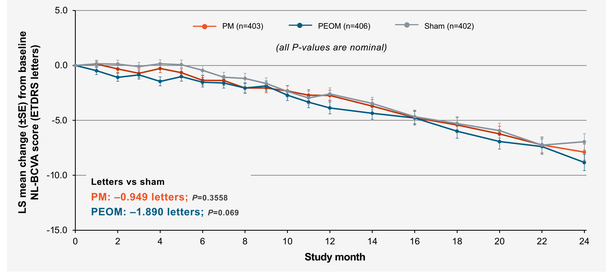


BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment of Diabetic Retinopathy Study; GA, geographic atrophy; LS, least square; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly.

Visual Function Endpoints

- There were no statistically significant differences across treatment arms in key functional outcomes, including BCVA (**Figure 5**) and microperimetry (OAKS only) (**Supplemental Figure 3; access via QR code**)

Figure 5. OAKS and DERBY Combined: BCVA in the Study Eye Over 24 Months



LS means estimated from MMRM analysis. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; GA, geographic atrophy; LS, least square; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; n, number of patients; NL, normal luminance; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly; SE, standard error.

Microperimetry: Post Hoc Analysis of the Junctional Zone

- *Post hoc* microperimetry analyses in the junctional zone of atrophy showed reduced loss of retinal sensitivity (mean threshold sensitivity: PM +0.564 decibel [dB], *P*=0.0650; PEOM +0.707 dB, *P*=0.0202) and fewer scotomatous points (PM –0.680 points, *P*=0.1444; PEOM –1.138 points, *P*=0.0140) (**Supplemental Figure 4; access via QR code**)

Safety

- Rates of treatment-emergent adverse events are shown in **Table 1**
- Intraocular inflammation and infectious endophthalmitis rates per injection were 0.20% (excluding four events in 2018 attributed to drug impurity) and 0.034%, respectively
- There were no reports of occlusive or nonocclusive vasculitis or retinitis
- In patients who developed new-onset study eye exudative age-related macular degeneration, the reading center classified choroidal neovascularization as occult in the vast majority (85.7%) of cases that could be assessed

Table 1. OAKS and DERBY Combined: TEAEs Over 24 Months

	PM (N=419)	PEOM (N=420)	Sham (N=417)
All TEAEs, n (%)	370 (88.3)	367 (87.4)	344 (82.5)
Ocular TEAEs in the study eye, patients, n (%)	258 (61.6)	231 (55.0)	193 (46.3)
Non-ocular TEAEs, patients, n (%)	337 (80.4)	307 (73.1)	300 (71.9)
Serious ocular TEAEs in the study eye, n (%)			
Endophthalmitis[a]	2 (0.5)	3 (0.7)	0
Optic ischemic neuropathy	3 (0.7)	0	0
Retinal detachment	1 (0.2)	1 (0.2)	0
Uveitis	0	2 (0.5)	0
Vitritis	2 (0.5)	0	0
Visual acuity reduced	0	1 (0.2)	1 (0.2)
Papilledema	1 (0.2)	0	0
Iridocyclitis	0	1 (0.2)	0
Retinal tear	1 (0.2)	0	0
Dry AMD	0	0	1 (0.2)
Macular hole	0	0	1 (0.2)
Hyphema	1 (0.2)	0	0
New-onset eAMD events in the study eye[b]			
Overall population, n/R (%)	51/419 (12.2)	28/419[c] (6.7)	13/417 (3.1)
Without fellow eye CNV at baseline, n/R (%)	37/335 (11.0)	19/338 (5.6)	5/330 (1.5)

Safety set. Sham patients do not receive injections. [a]Includes events of both infectious and non-infectious endophthalmitis. [b]eAMD events were investigator-determined and include preferred terms of CNV and neovascular AMD. [c]Number of patients at risk for new-onset eAMD in PEOM arms from OAKS and DERBY combined was 419.
AMD, age-related macular degeneration; CNV, choroidal neovascularization; eAMD, exudative AMD; n/R, number of patients affected/number of patients at risk; PEOM, pegcetacoplan every other month; PM, pegcetacoplan monthly; TEAE, treatment-emergent adverse event.

Conclusions

- Pegcetacoplan is the first and only drug approved in the US for the treatment of GA (US Food and Drug Administration approval, February 17, 2023) and an investigational drug under regulatory review by the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency
- Pegcetacoplan slowed GA progression with both PM and PEOM dosing, with increasing effects over time
- Reductions in GA lesion growth were consistent and treatment benefit was observed across all prespecified subgroups, including those with nonsubfoveal and subfoveal lesions and those with unifocal and multifocal lesions
- A signal of functional benefit was observed in microperimetry analyses of the junctional zone
- Pegcetacoplan was well tolerated, with mostly mild to moderate ocular study eye adverse events
- The GALE extension study will report the long-term impact of treatment with pegcetacoplan

References

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Contact information:
Ian Pearce: Ian.Pearce@liverpoolft.nhs.uk