Assessment of geographic atrophy progression in the phase 3 OAKS and DERBY trials

Components of the complement system, including C3, have been detected in drusen and age-related macular degeneration (AMD) lesions. The Phase 3 OAKS and DERBY trials demonstrate the safety and efficacy of pegcetacoplan, which targets C3, in reducing geographic atrophy (GA) lesion growth.

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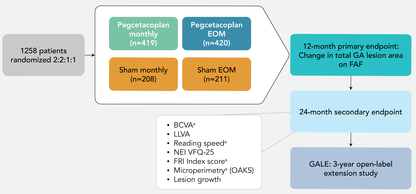
Patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) were randomized across 232 sites.



Inclusion criteria

- Age ≥60 years
- BCVA ≥24 letters ETDRS (20/320 Snellen equivalent)
- GA lesion requirements:
  - Total size: ≥2.5 and ≤17.5 mm^2; if multifocal, at least one focal lesion must be ≥1.25 mm^2 (0.5 DA)
  - Presence of perilesional hyperautofluorescence
  - GA lesions with or without subfoveal involvement allowed

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

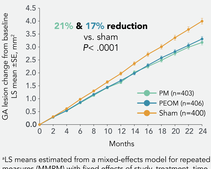
*Key secondary endpoints.

OAKS, DERBY, GALE CT.gov identifiers: NCT03525613, NCT03525600, NCT04770545, respectively.

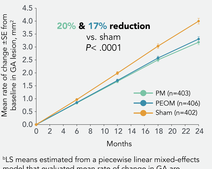
AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; DA = disc area; EOM = every other month; ETDRS = Early Treatment Diabetic Retinopathy Study; FAF = fundus autofluorescence; FRI = Functional Reading Independence; GA = geographic atrophy; LL = low luminance; NEI-VFQ = National Eye Institute Visual Function Questionnaire; RPE = retinal pigment epithelium.

Pegcetacoplan reduced GA lesion growth in OAKS & DERBY combined.

MMRM analysis (primary)[a]



Piecewise linear slope analysis (post hoc)[b]



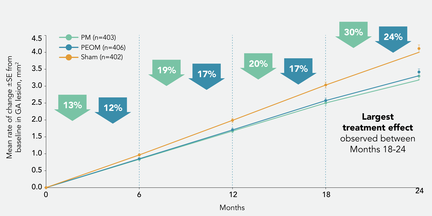
[a]LS means estimated from a mixed-effects model for repeated measures (MMRM) with fixed effects of study, treatment, time, treatment × time interaction, baseline GA lesion area strata, fellow eye CNV, and baseline GA lesion strata × time interaction.

[b]LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA are between pegcetacoplan arms and sham arm from baseline to Month 24, with knots at Months 6, 12 & 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis).

Analysis performed on mITT population, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline study eye GA lesion area value. Includes 1 patient in each of OAKS Sham, DERBY Pegcetacoplan EOM, and DERBY Sham groups and had their first postbaseline GA lesion assessment after month 12.

EOM = every other month; GA = geographic atrophy; LS = least squares; mITT = modified intent to treat; PM = pegcetacoplan monthly; PEOM = pegcetacoplan every other month.

Pegcetacoplan reduced mean rate of GA growth with increasing treatment effect over time.



Percent reductions vs sham pooled between Month 0 and Month 24 were estimated from a piecewise linear slope model with 6-month segments.
GA = geographic atrophy; LS = least square; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SE = standard error.

Adverse events of interest at 24 months include exudative AMD, optic ischaemic neuropathy, and intraocular inflammation.

	PM (n=419)	PEOM (n=420)	Sham (n=417)
Exudative AMD*			
*Includes adverse events reported by the investigator as choroidal neovascularization or neovascular AMD.	12%	7%	3%
Optic ischaemic neuropathy (OIN)**			
SAEs	3	0	0
AEs	4	1	0
Total rate	1.7%	0.2%	0%

**All patients with OIN had discs at risk and multiple systemic risk factors

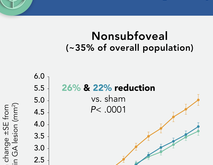
Intraocular inflammation

28 cases out of 11,736 pegcetacoplan injections → 0.24% per injection

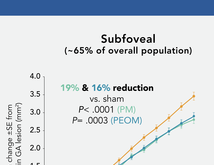
No events of occlusive vasculitis or retinitis reported

Reductions in GA lesion growth by lesion location were observed.

Nonsubfoveal (~35% of overall population)



Subfoveal (~65% of overall population)



LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat 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.

EOM = every other month; GA = geographic atrophy.

Conclusions

Pegcetacoplan is the first and only FDA-approved treatment for GA secondary to AMD.

Pegcetacoplan slows GA progression with both monthly and every other month dosing, with effects increasing over time

- Treatment benefit demonstrated across all pre-specified subgroups

In the quartile analysis, Quartile 1 (slow progressors) had a higher proportion of patients from PM and PEOM arms versus sham. Conversely, Quartile 4 (fast progressors) had a higher proportion of sham patients than PM or PEOM.

Based on the area of retinal tissue preserved, between 3500–10,000 RPE are saved with 2 years of treatment, which corresponds with a much larger number of PR cells saved.

Pegcetacoplan demonstrated visual function and quality of life benefits vs sham in patients with lesions further from the fovea.