

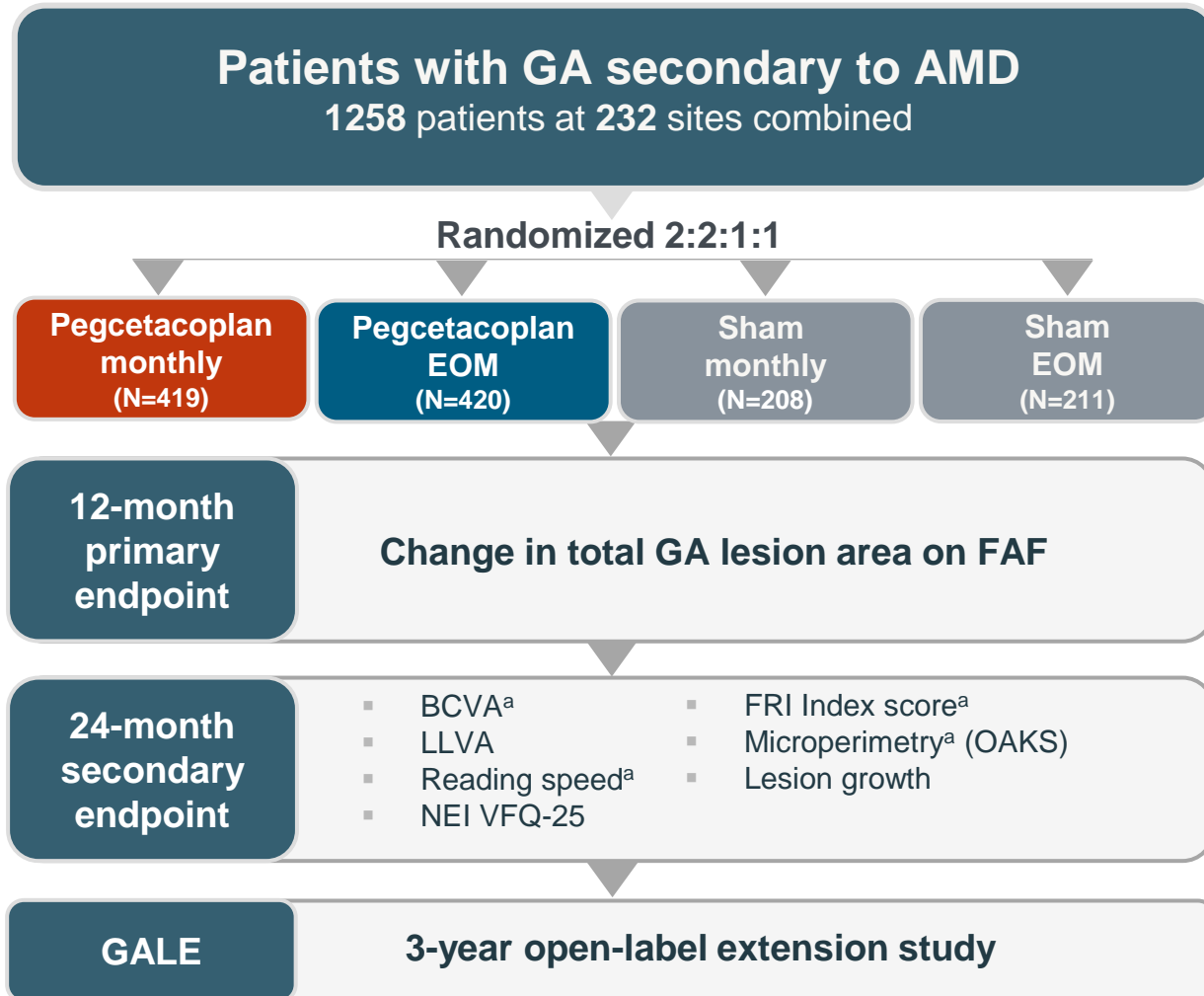
Assessment of geographic atrophy progression in the phase 3 OAKS and DERBY trials

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Phase 3 OAKS and DERBY trials: Design 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

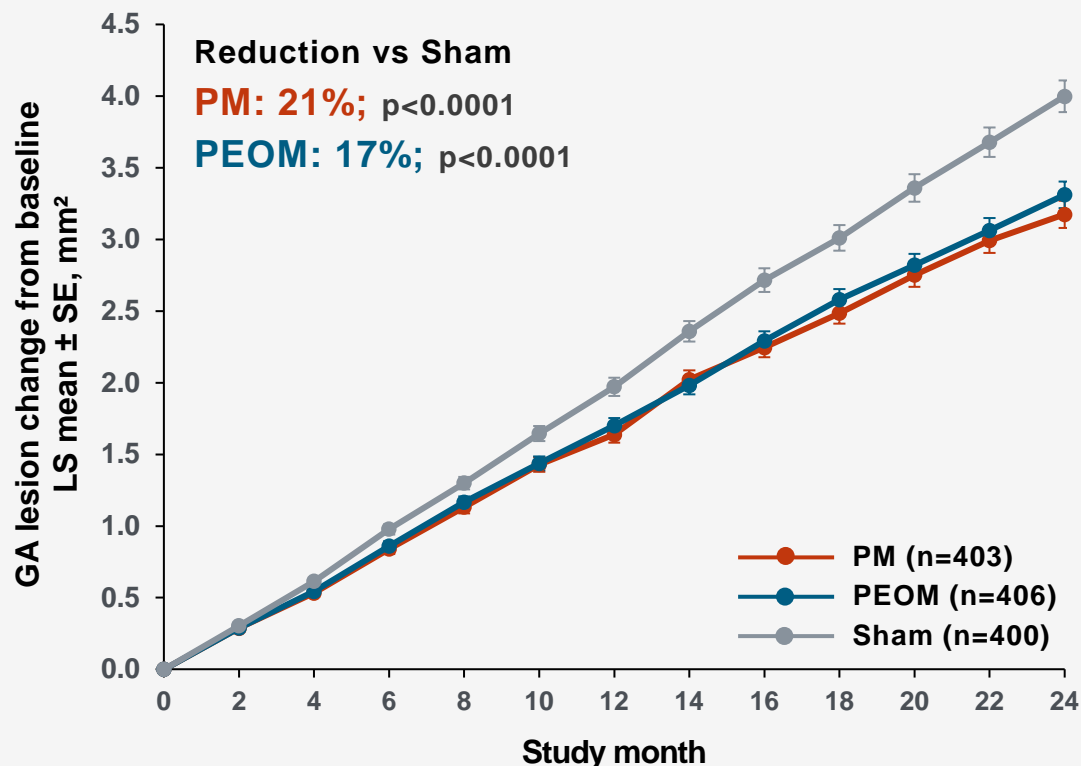
- GA secondary to a condition other than AMD, such as Stargardt disease, in either eye
- CNV in the study eye (active or history of), including presence of RPE tear (assessed by reading center)

CNV in the fellow eye was not exclusionary

OAKS, DERBY, GALE CT.gov identifiers: NCT03525613, NCT03525600, NCT04770545, respectively. ^aKey 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; LL=low luminance; NEI-VFQ=National Eye Institute Visual Function Questionnaire; RPE=retinal pigment epithelium.

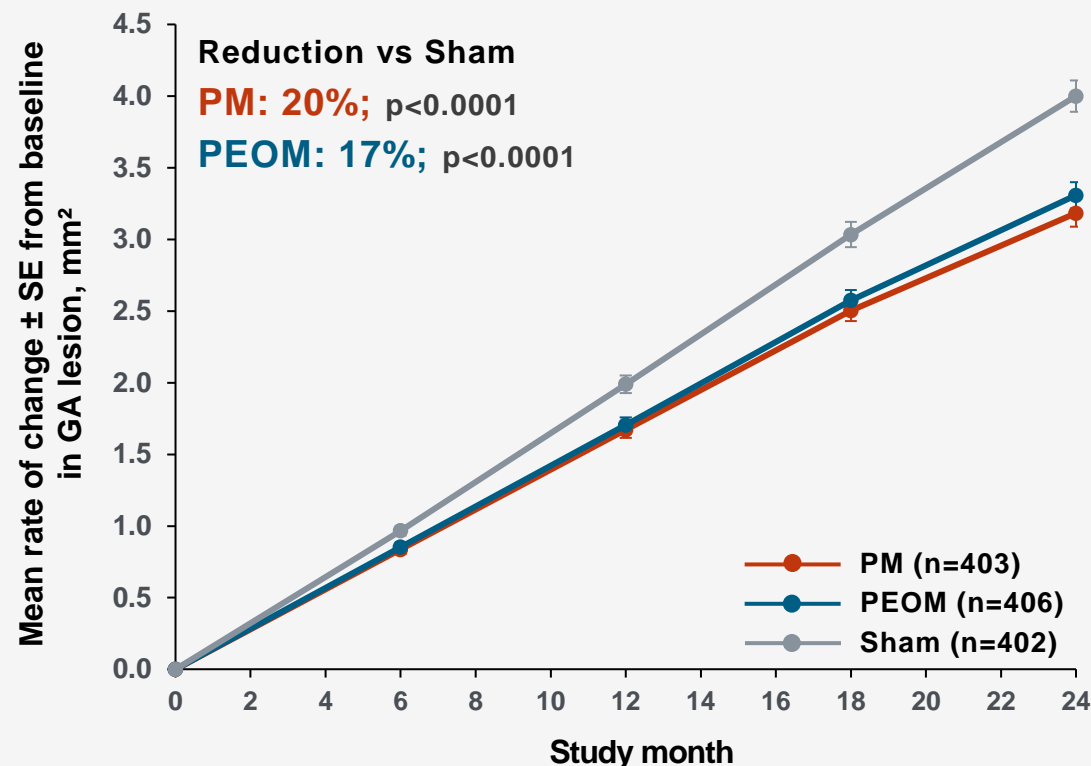
Pegcetacoplan reduced GA lesion growth

MMRM analysis (primary)



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

Piecewise linear slope analysis (*post hoc*)



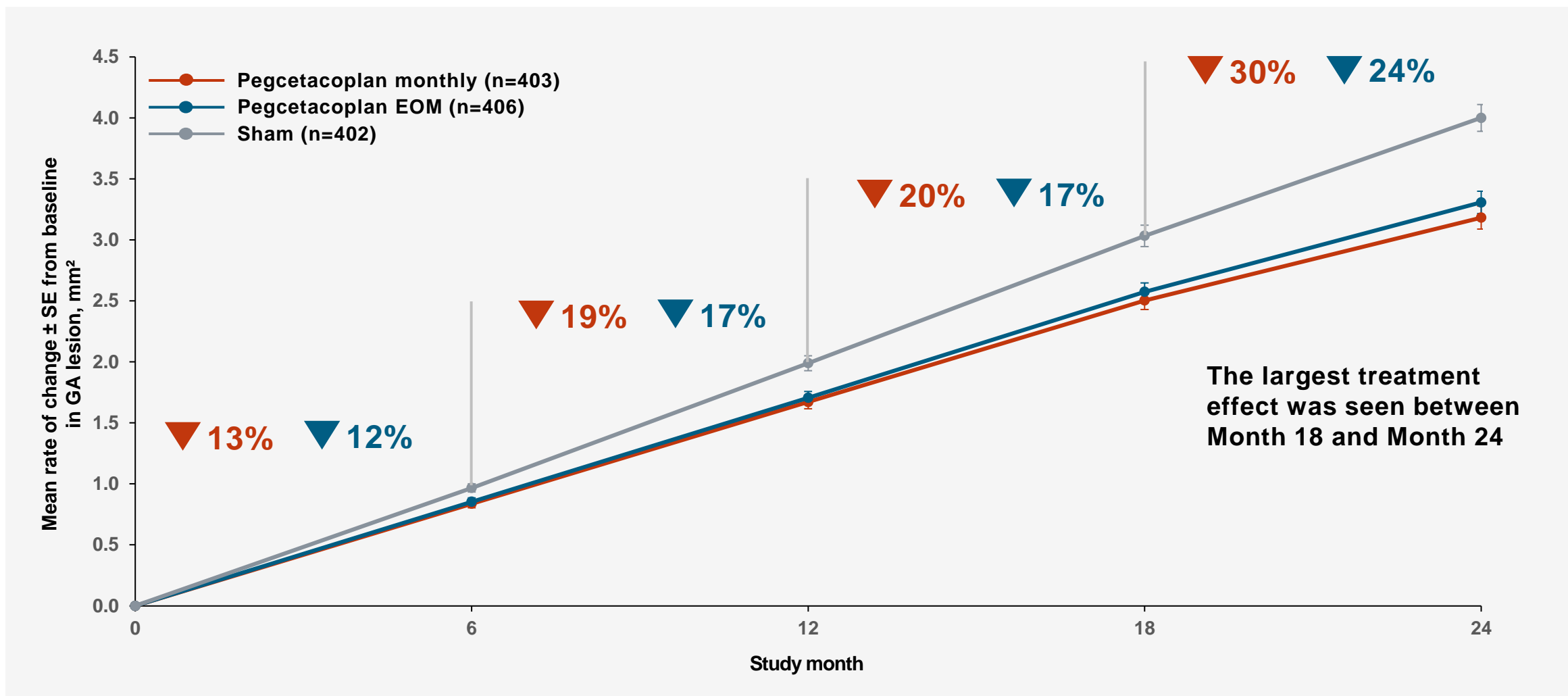
LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 24, with knots at Months 6, 12 & 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments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

(all p-values are nominal)

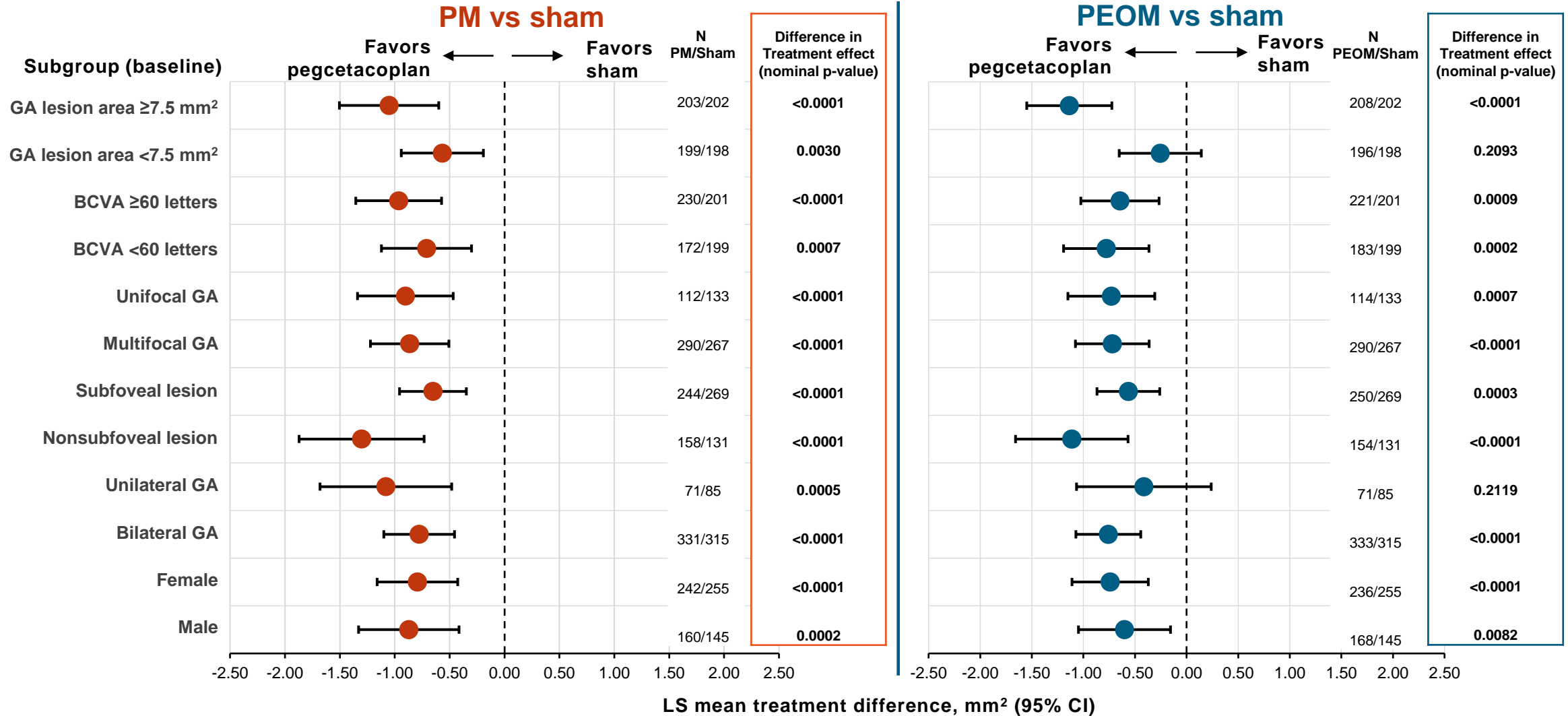
Analysis performed on mITT population, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline study eye GA lesion area value. Includes 1 patient in each of OAKS-Sham, DERBY-Pegcetacoplan EOM, and DERBY-Sham groups and had their first postbaseline GA lesion assessment after month 12. OAKS, NCT03525613; DERBY, NCT03525600. EOM, every other month; GA, geographic atrophy; LS, least squares; mITT, modified intent-to-treat; PM, pegcetacoplan monthly; PEOM, pegcetacoplan every-other-month.

OAKS and DERBY combined

Increasing treatment effect over time



Treatment effect on GA lesion growth across subgroups



Adverse events of interest at 24 months

EXUDATIVE AMD*	
PM (n=419)	12%
PEOM (n=420)	7%
Sham (n=417)	3%

OPTIC ISCHAEMIC NEUROPATHY			
	SAEs	AEs	Total rate
PM (n=419)	3	4	1.7%
PEOM (n=420)	0	1	0.2%
Sham (n=417)	0	0	0%

INTRAOCULAR INFLAMMATION

28 cases out of 11,736 pegcetacoplan injections

0.24% per injection

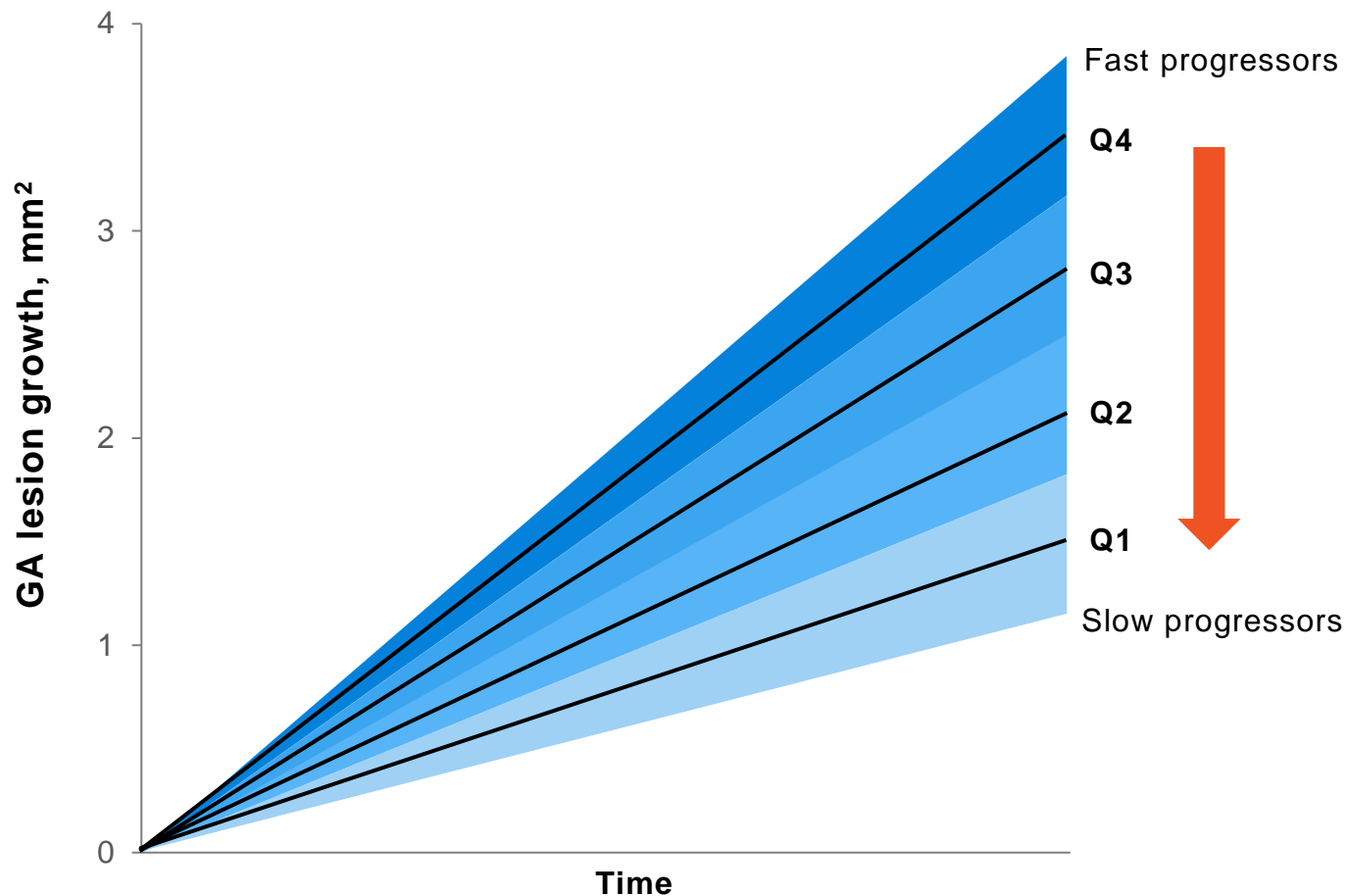
No events of occlusive vasculitis or retinitis were reported

- All cases were evaluated by neuro-ophthalmologists
- All patients with OIN had discs at risk and multiple systemic risk factors

*Exudative AMD includes adverse events reported by the investigator as choroidal neovascularization or neovascular AMD.
 AEs=adverse events; AMD=age-related macular degeneration; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SAEs=serious adverse events.

Post hoc analysis of OAKS and DERBY: Quartile analysis of GA lesion growth over 24 months

Schematic representation of progression



Is pegcetacoplan treatment associated with a shift in distribution of patients into slower progressing quartiles?

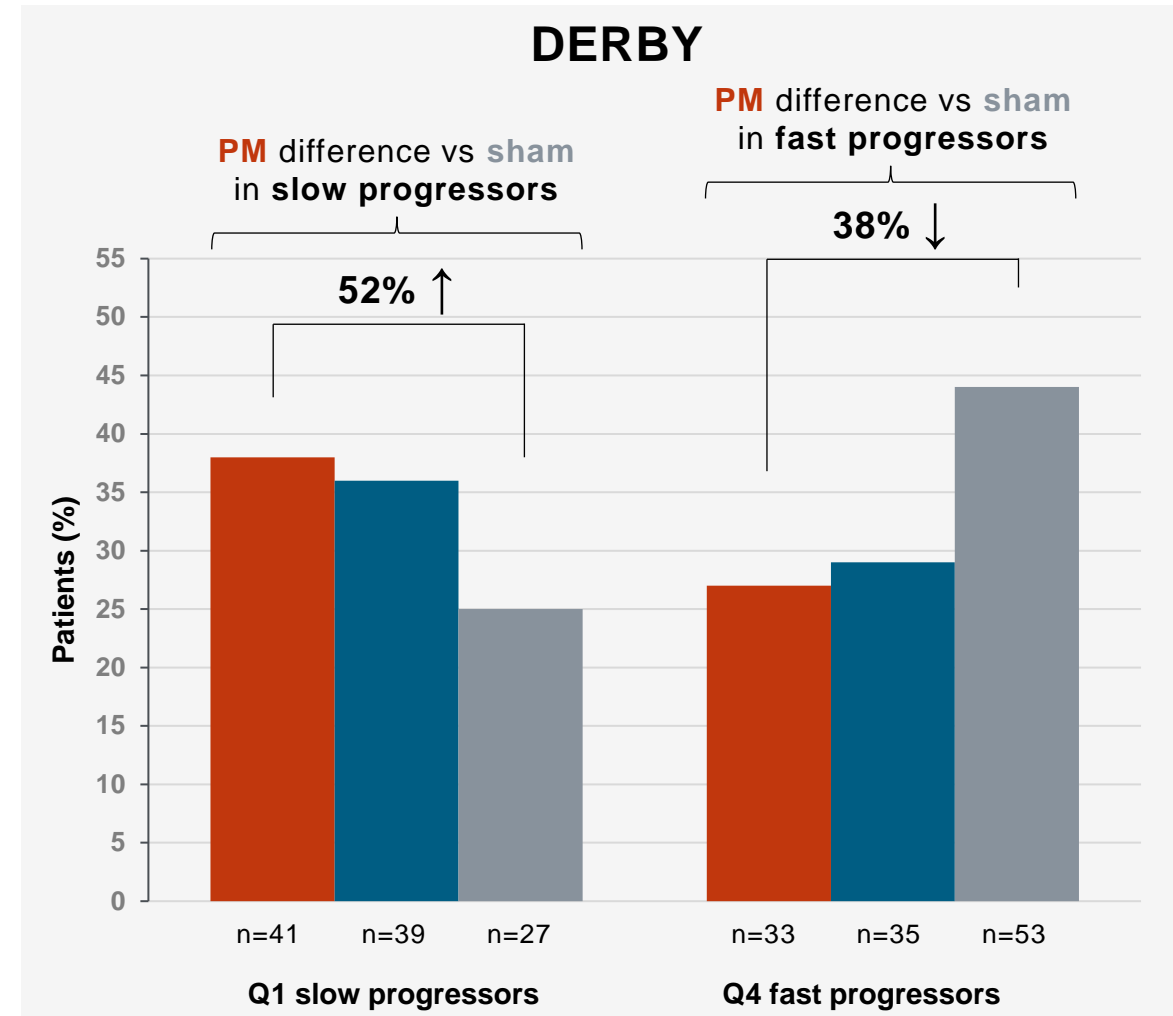
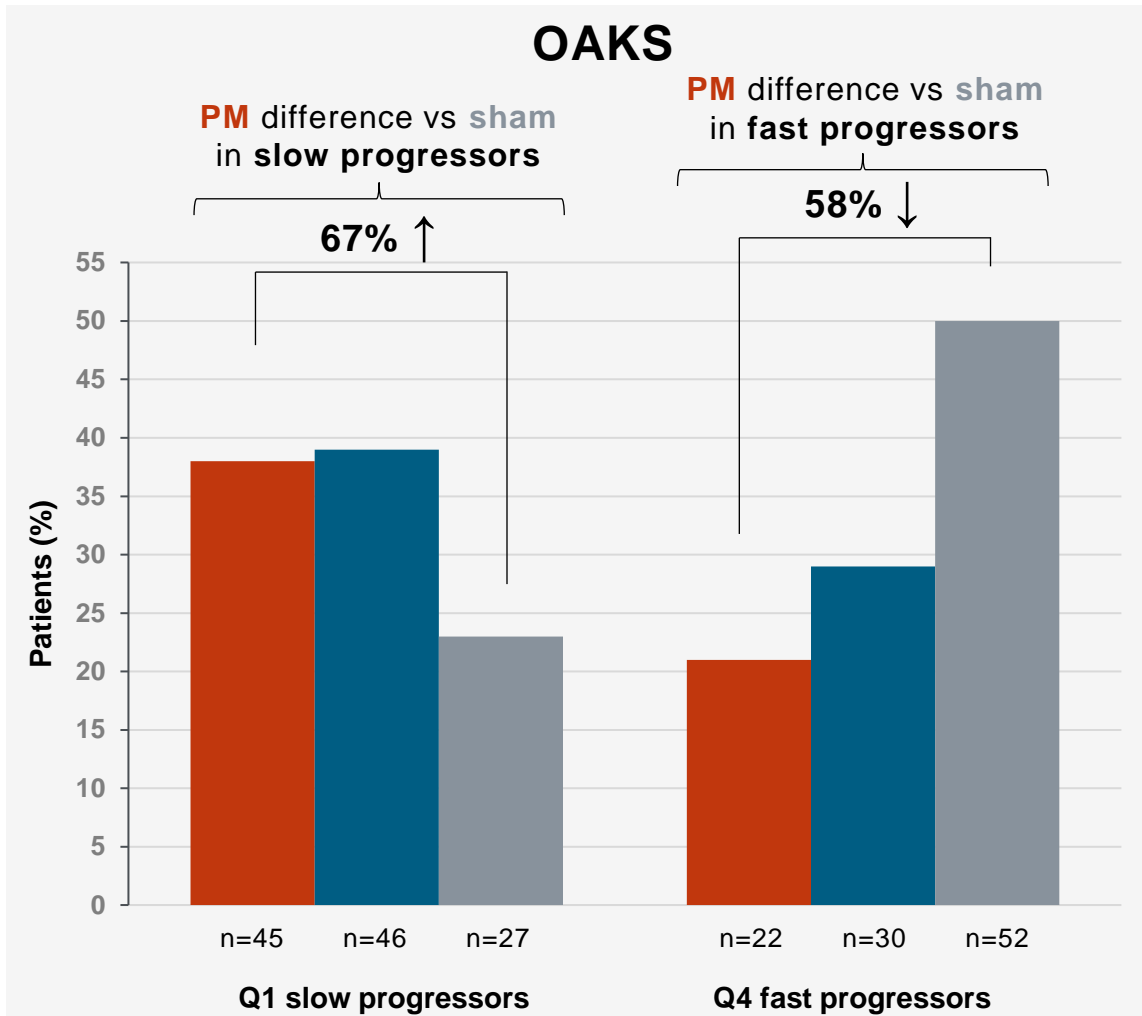
Post hoc analysis: Methods and quartile definitions

GA progression measured by change in lesion area (mm²) from baseline to Month 24

- GA progression **by quartiles of growth** assessed in the overall patient population
- Patients needed to have a Month 24 lesion growth measurement to be included in the analysis
- Total n=1000; 250 per quartile

Lesion growth quartiles	Growth over 2 years (mm ²)
Quartile 1 slowest progressors	≤2.08
Quartile 2	>2.08–≤3.13
Quartile 3	>3.13–≤4.53
Quartile 4 fastest progressors	>4.53

Distribution of patients by study arm across quartiles reflects efficacy of pegcetacoplan at 24 months

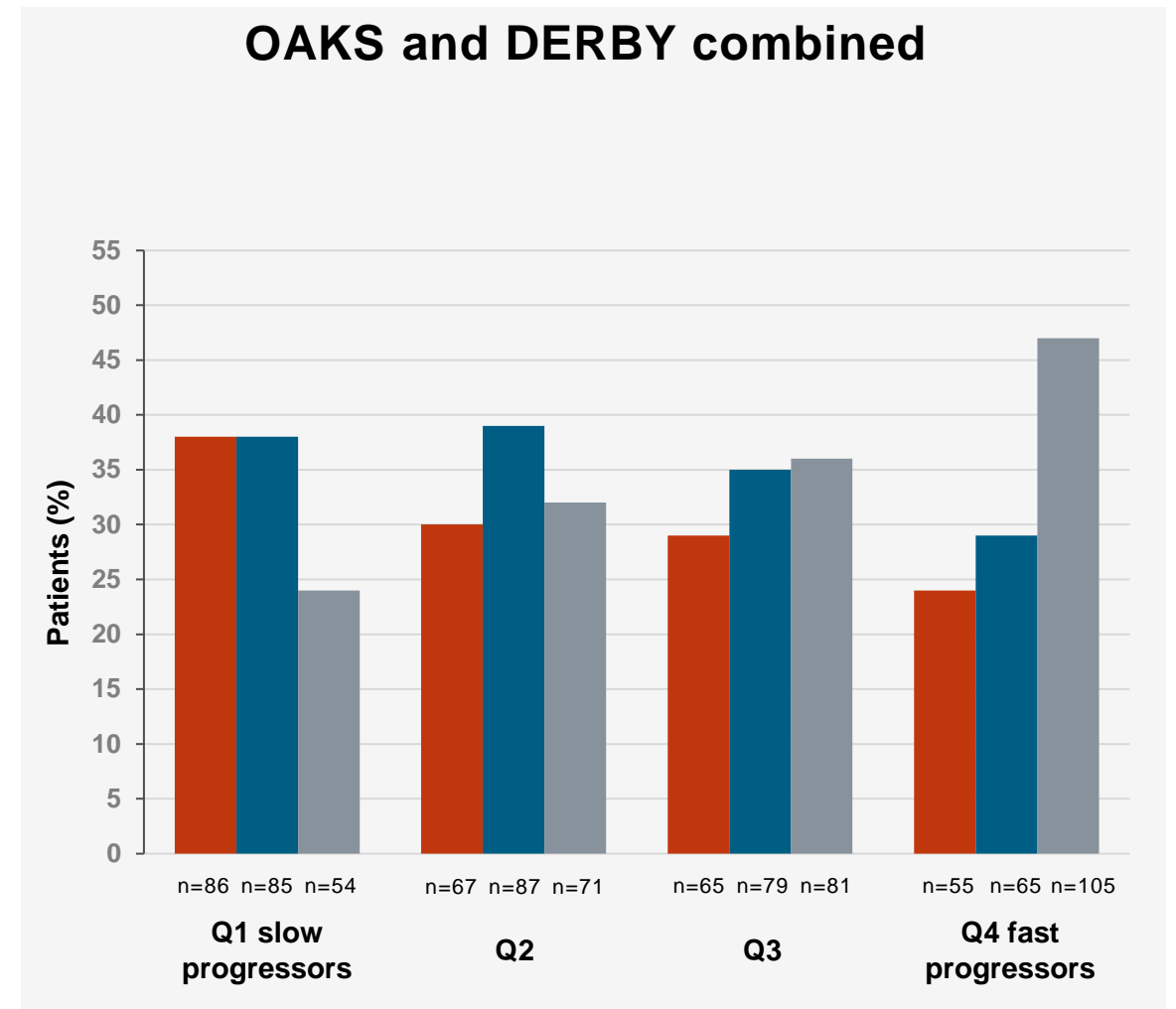
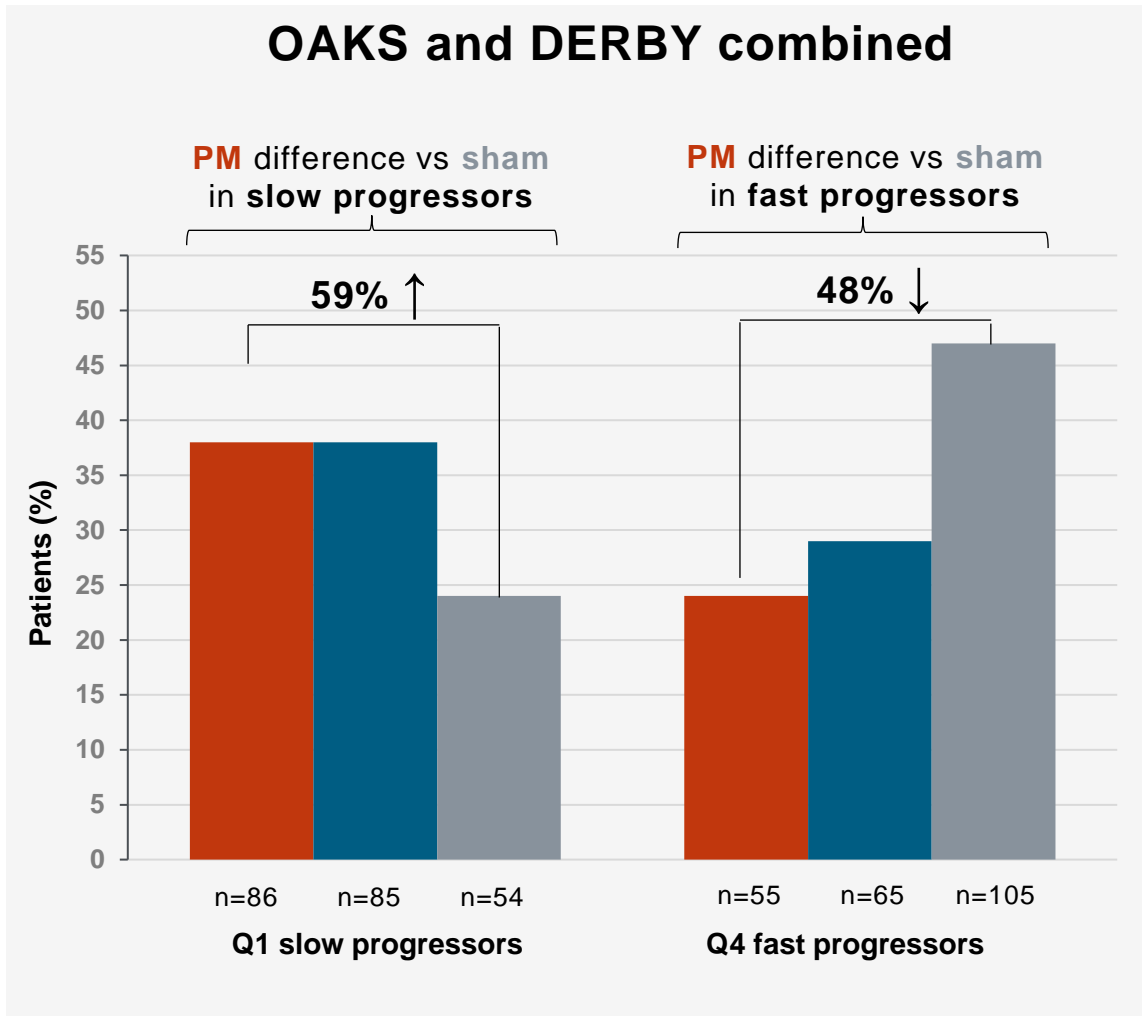


PM

PEOM

Sham pooled

Distribution of patients by study arm across quartiles reflects efficacy of pegcetacoplan at 24 months

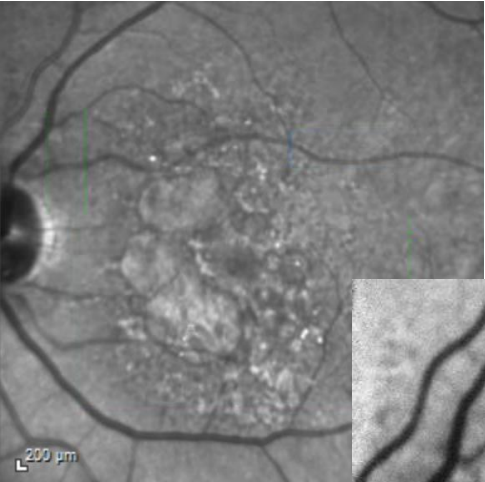


PM

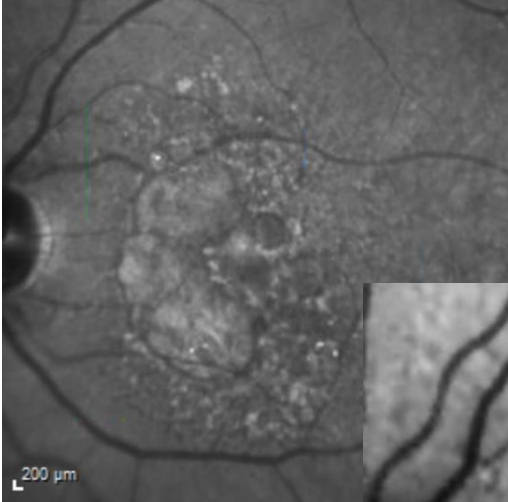
PEOM

Sham pooled

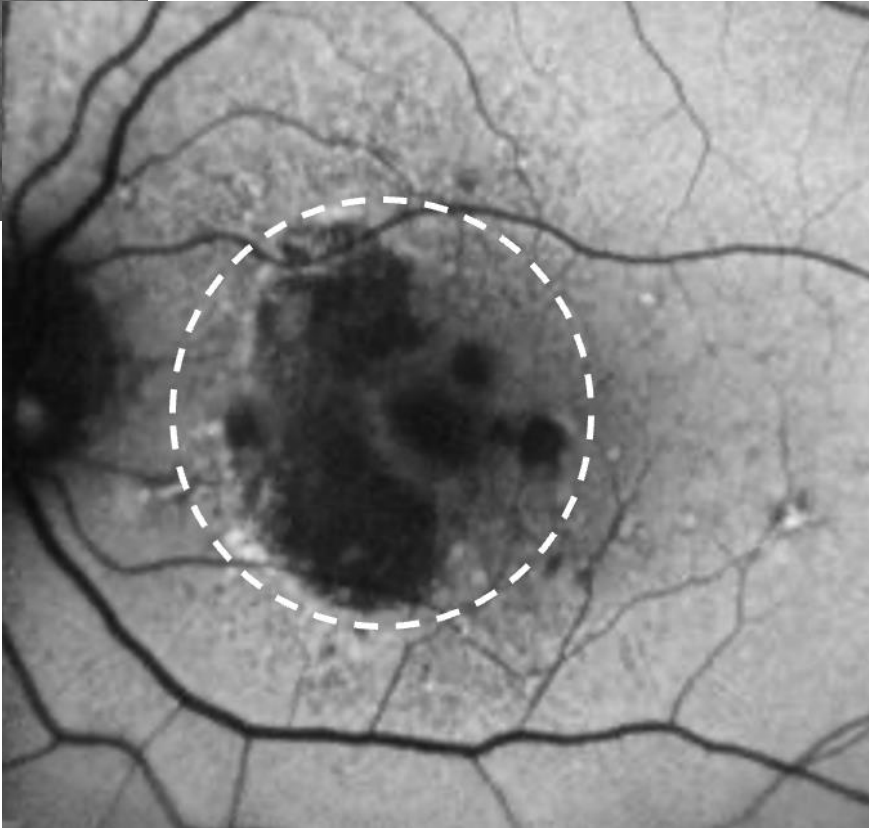
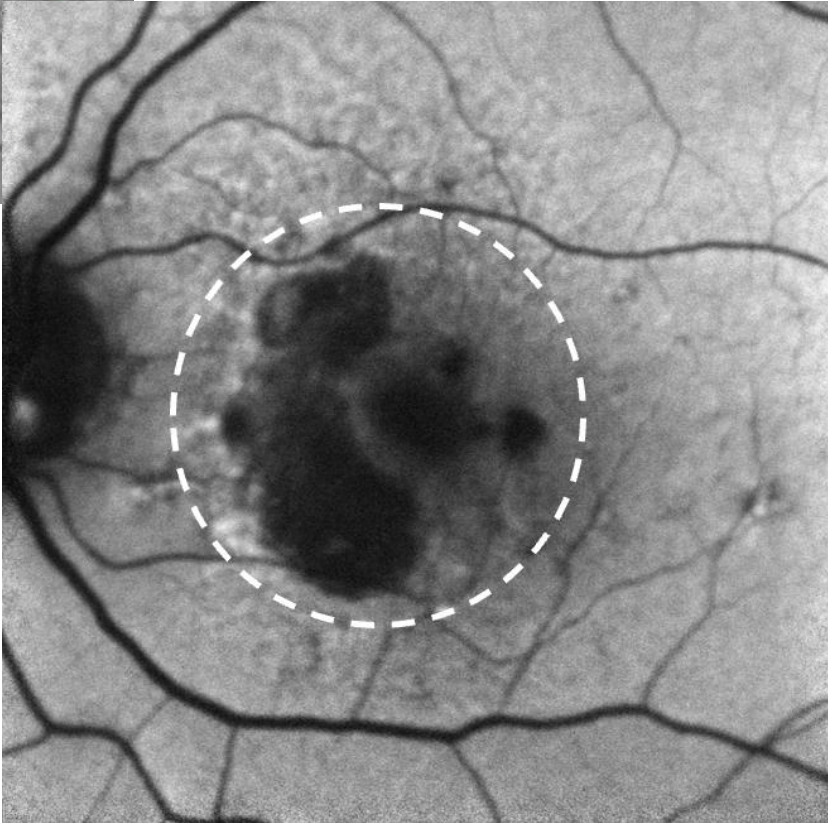
Example of GA lesion growth of 1.15 mm² on FAF



4.58 mm²



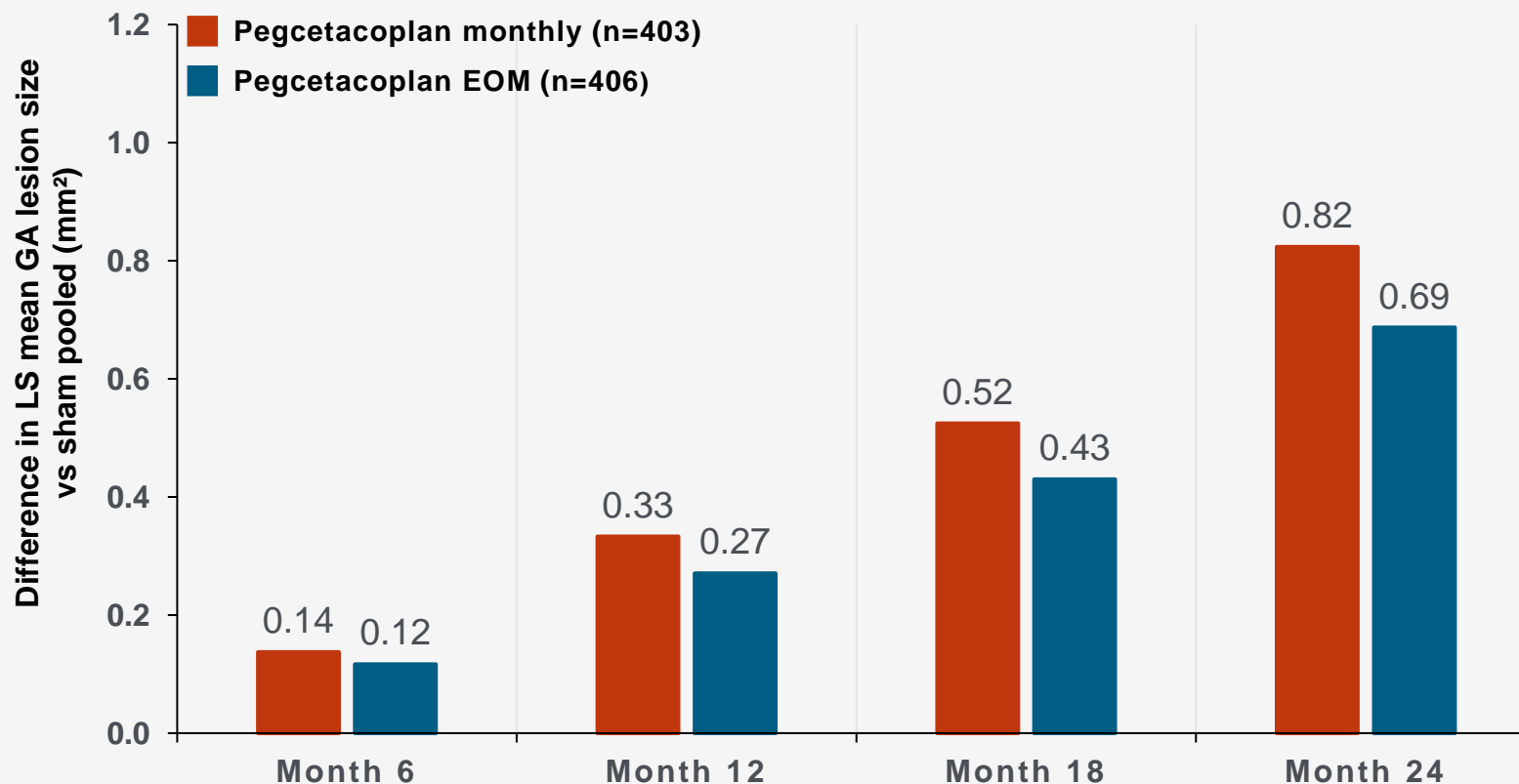
5.73 mm²



FAF=fundus autofluorescence.

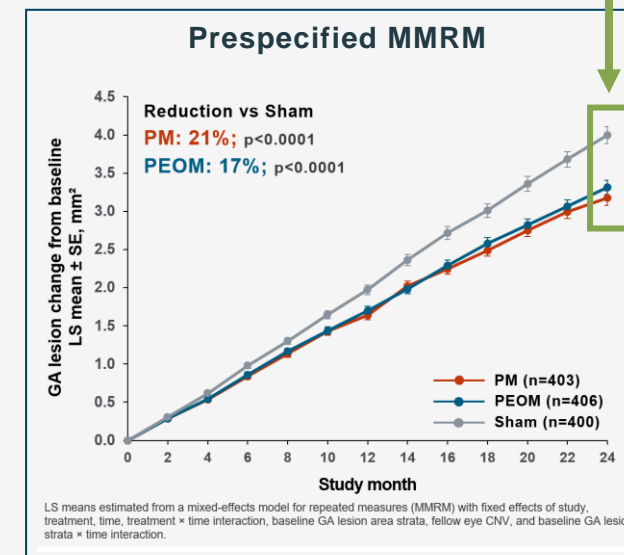
Amount of retina tissue preserved (mm²) with pegcetacoplan treatment

OAKS and DERBY combined



Difference vs sham in GA lesion area at 24 months

PM: 0.82 mm²
PEOM: 0.69 mm²



Absolute cumulative difference in lesion size vs pooled sham at Month 6, Month 12, Month 18, and Month 24 ('preserved area') from main MMRM 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 who had their first postbaseline GA lesion assessment after month 12. OAKS, NCT03525613; DERBY, NCT03525600. EOM, every other month; GA, geographic atrophy; LS, least squares; mITT, modified intent-to-treat.

Retinal tissue and RPE cells preserved* with pegcetacoplan

OAKS and DERBY combined

**Pegcetacoplan monthly
(n=403)**

**Pegcetacoplan EOM
(n=406)**

6-month intervals	Retinal tissue saved (mm ²)	RPE cells saved
0–6 months	0.14	700–1100
6–12 months	0.20	1000–1500
12–18 months	0.19	1000–1500
18–24 months	0.30	1500–2300
Total over 24M^a	0.82	4200–6300

**4200–6300
RPE CELLS SAVED*
at 24 months**
**with pegcetacoplan
monthly**

**3500–5300
RPE CELLS SAVED*
at 24 months**
**with pegcetacoplan
EOM**

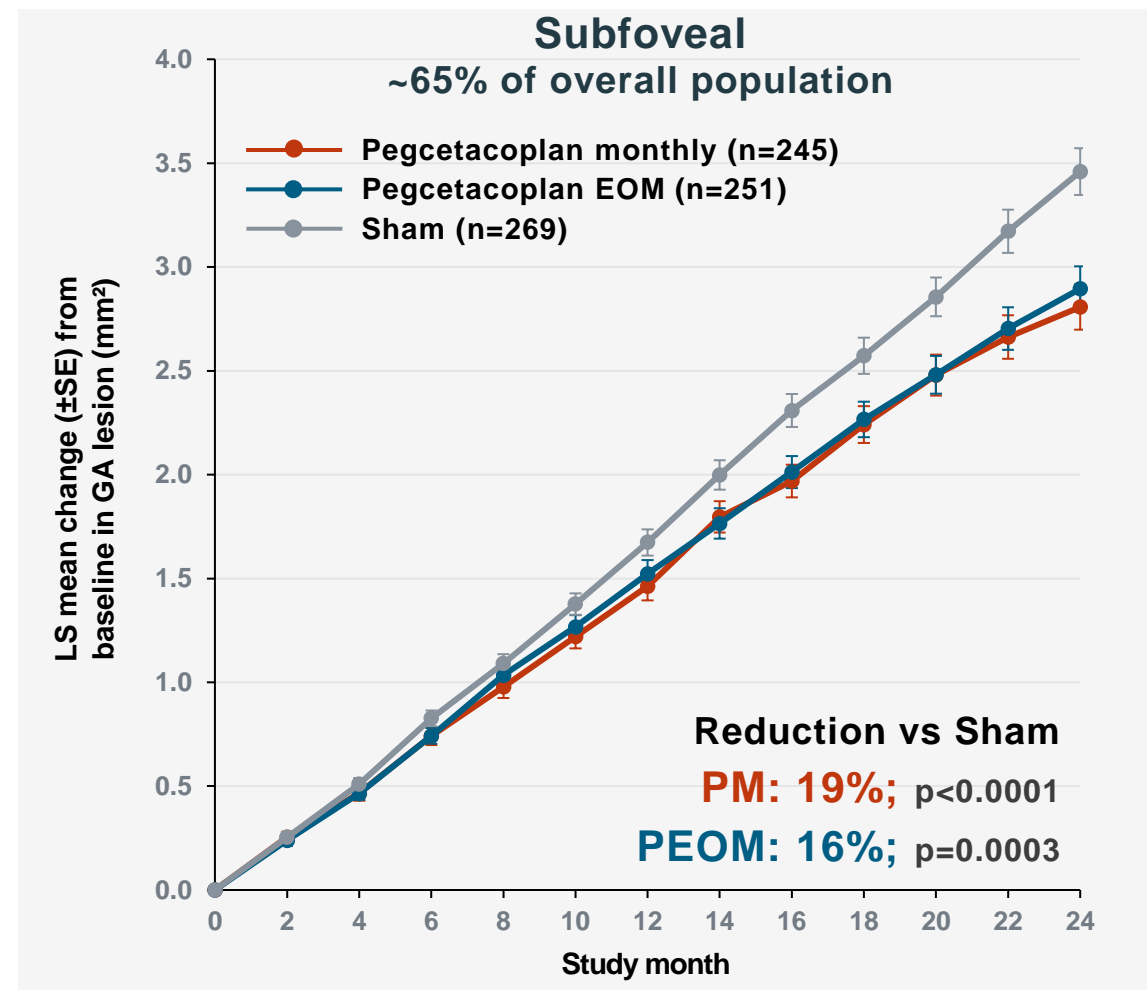
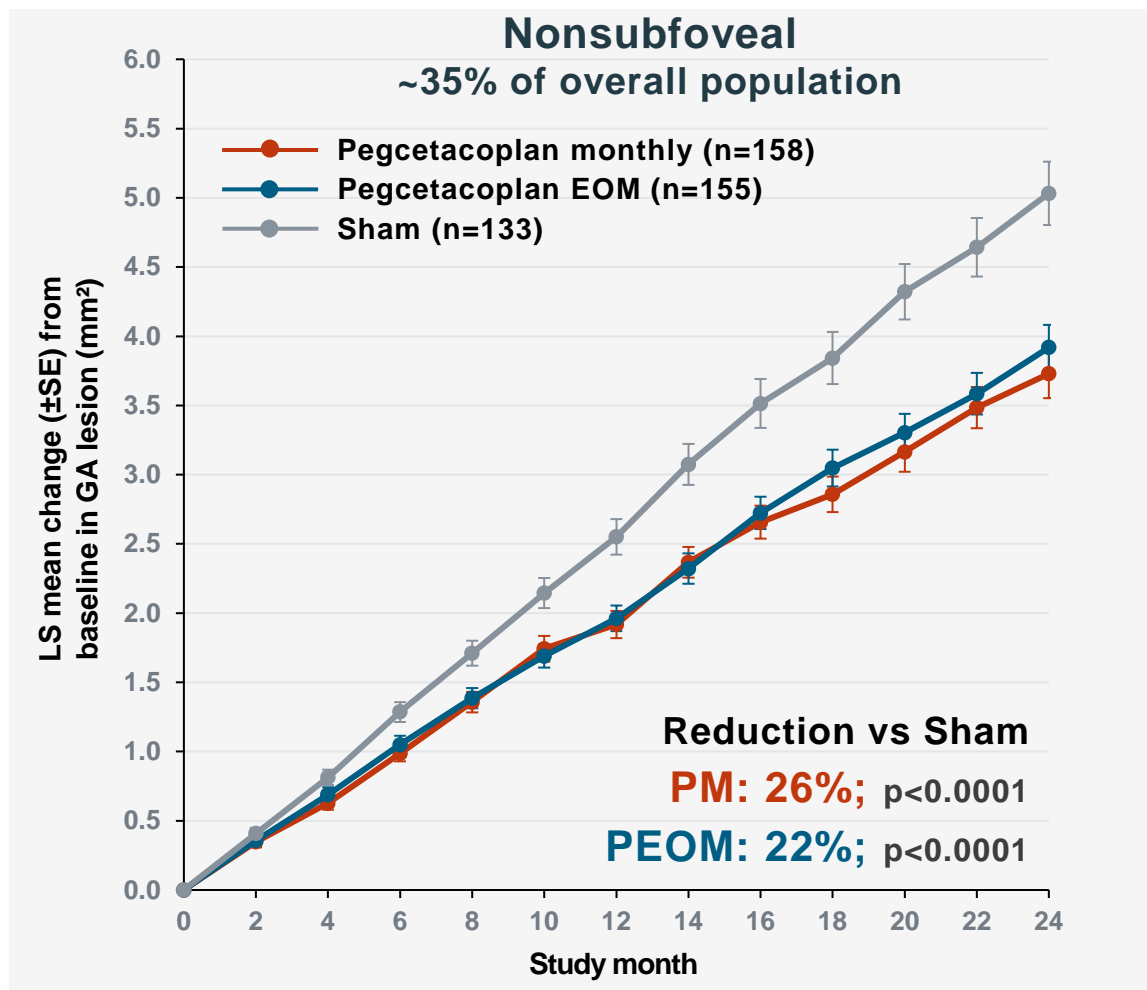
Retinal tissue saved (mm ²)	RPE cells saved
0.12	600–900
0.15	800–1200
0.16	800–1200
0.26	1300–2000
0.69	3500–5300

*Estimated based on macular RPE density¹ range of 5082 cells/mm² to 7728 cells/mm²

^aNumbers may differ slightly from total of 6-month intervals due to rounding.

1. Ach T et al. *Invest Ophthalmol Vis Sci.* 2014;55:4832–4841. EOM, every other month; RPE, retinal pigment epithelium.

Reductions in GA lesion growth by lesion location

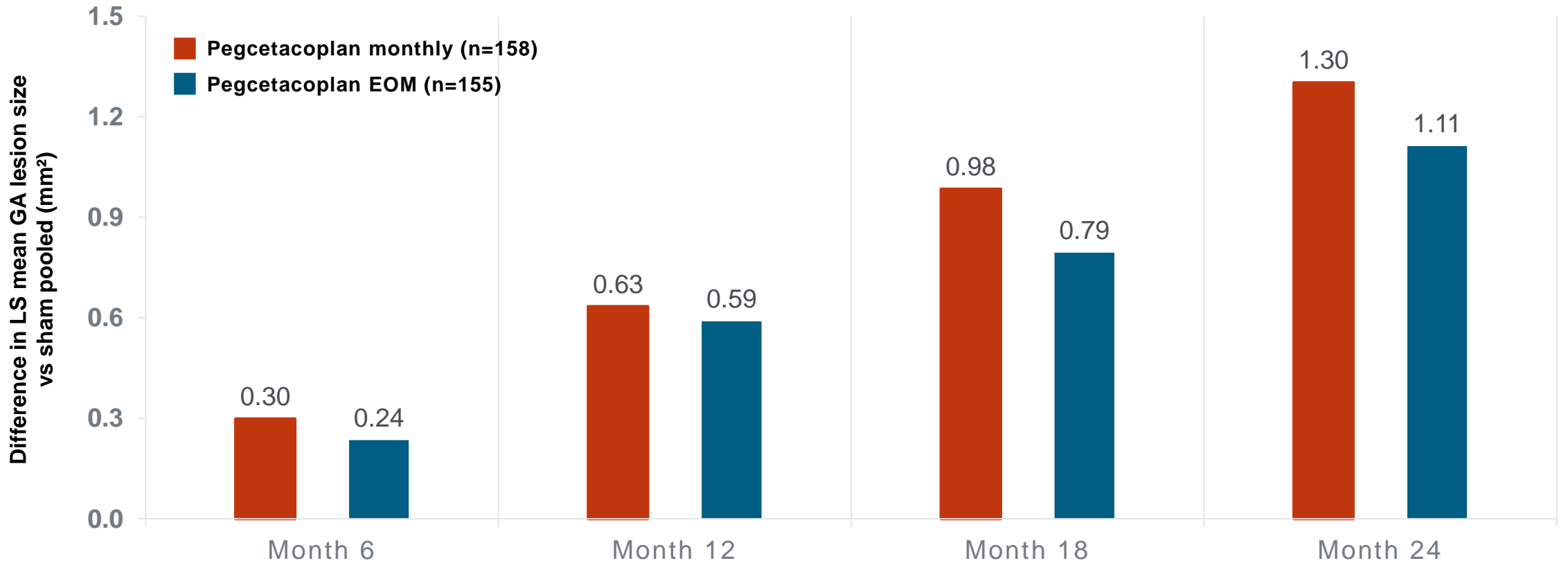


(all p-values are nominal)

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; LS=least square; SE=standard error.

OAKS and DERBY combined

Cumulative preservation of retinal tissue in nonsubfoveal lesions



Absolute cumulative difference in lesion size vs pooled sham at Month 6, Month 12, Month 18, and Month 24 ('preserved area') from main MMRM analysis of mITT population. Fovea size calculated from average diameter of 1.5 mm per Kolb et al., *The Architecture of the Human Fovea*. EOM=every other month; GA=geographic atrophy; NSF=nonsubfoveal; PM=pegcetacoplan monthly. mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures.

Retinal tissue and RPE cells preserved* with pegcetacoplan: Nonsubfoveal subgroup

OAKS and DERBY combined

**Pegcetacoplan monthly
(n=158)**

**Pegcetacoplan EOM
(n=155)**

6-month intervals	Retinal tissue saved (mm ²)	RPE cells saved
0–6 months	0.30	1500–2300
6–12 months	0.34	1700–2600
12–18 months	0.35	1800–2700
18–24 months	0.32	1600–2500
Total over 24M^a	1.30	6600–10,000

**6600–10,000
RPE CELLS SAVED*
at 24 months
with pegcetacoplan
monthly**

**5600–8600
RPE
CELLS SAVED*
at 24 months
with pegcetacoplan
EOM**

Retinal tissue saved (mm ²)	RPE cells saved
0.24	1200–1900
0.35	1800–2700
0.21	1100–1600
0.32	1600–2500
1.11	5600–8600

*Estimated based on macular RPE density¹ range of 5082 cells/mm² to 7728 cells/mm²

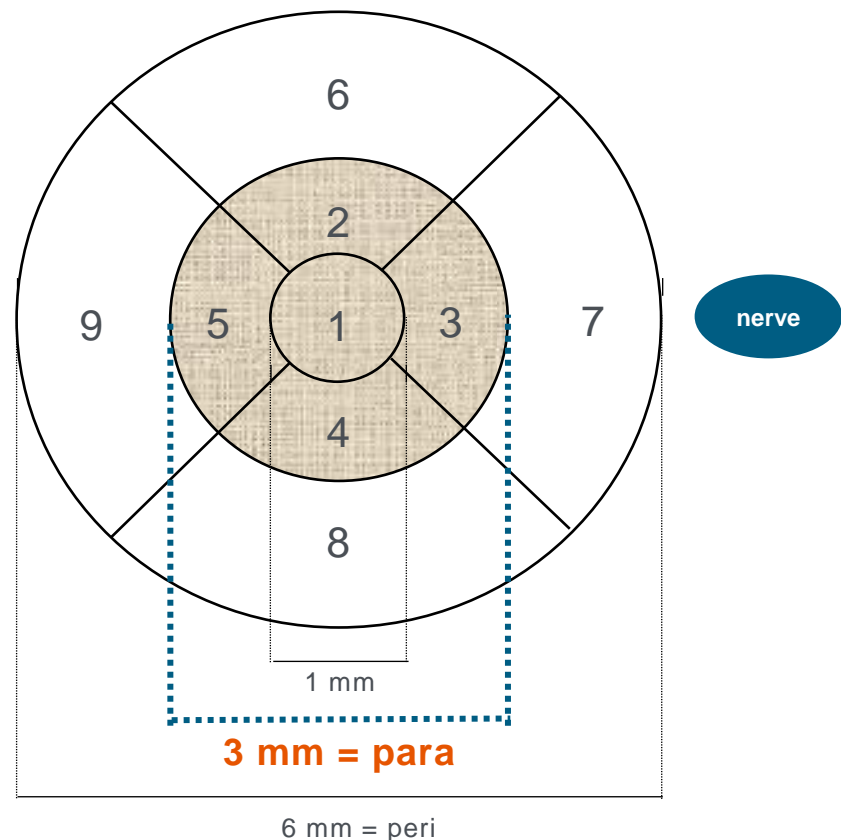
^aNumbers may differ slightly from total of 6-month intervals due to rounding. Nonsubfoveal defined as GA lesion border >0 μm from center point of the fovea. 1. Ach T et al. *Invest Ophthalmol Vis Sci* 2014;55:4832–4841. EOM=every other month; RPE, retinal pigment epithelium.

Functional data by lesion distance from the foveal center

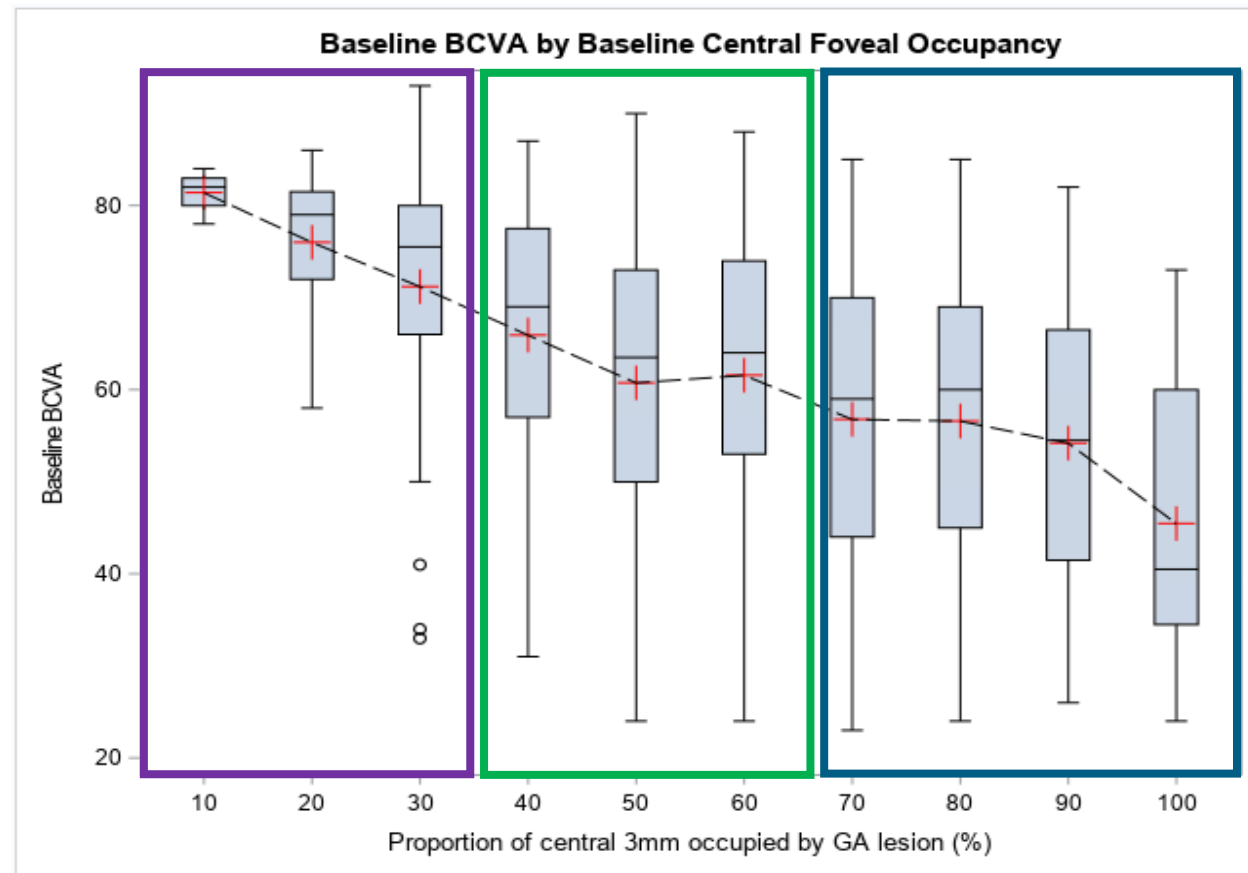
Post hoc subgroup analyses

- **Subgroups:** ≥ 250 μm and < 250 μm from the foveal center
- **Data Source:** AI-based automated segmentation of RPE loss from OAKS and DERBY patients with Spectralis (Heidelberg) OCT Images (~75% total sample size)
- **Model specification and baseline covariate selection were done *a priori*** based on clinical rationale^{1,2}: demographics, study eye characteristics (including foveal occupancy of regions 1–5), and fellow eye characteristics

BCVA is correlated with the proportion of the fovea (ETDRS regions 1-5) occupied by GA lesion



- **Foveal Occupancy:** proportion of the central subfield and the inner ring of the ETDRS grid (regions 1-5) occupied by the GA lesion

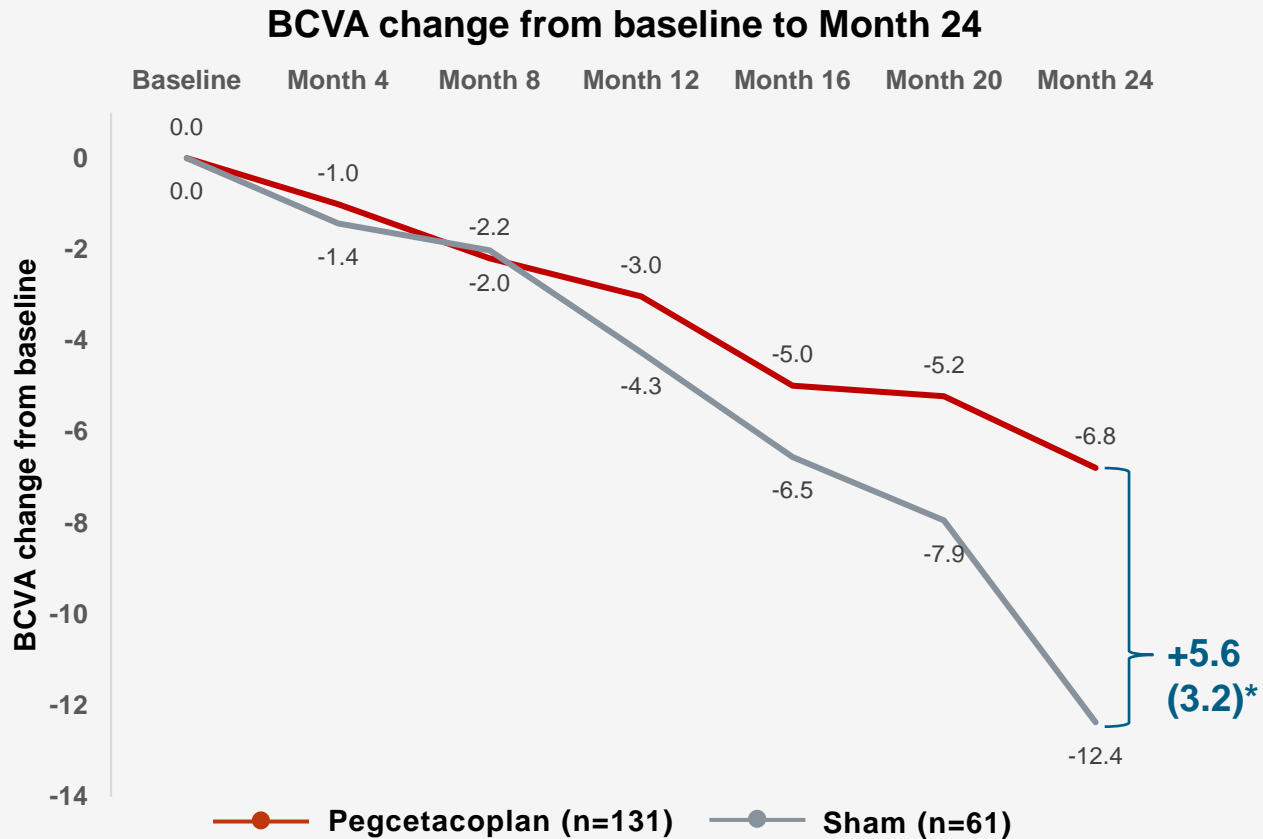


- **OAKS and DERBY Baseline Data:** increasing levels of central 3 mm foveal region occupancy showed a trend toward lower BCVA scores*

*Analysis only included patients with OCT images from SPECTRALIS® machines (~75% of OAKS and DERBY sample).
 BCVA=best-corrected visual acuity; GA=geographic atrophy; OCT=optical coherence tomography; RPE=retinal pigment epithelium.

Pegcetacoplan was associated with slower vision loss and better quality of life in patients with lesions $\geq 250\mu\text{m}$ away from the foveal center

Baseline BCVA: PEG 73 and Sham 75 (~20/32 Snellen)



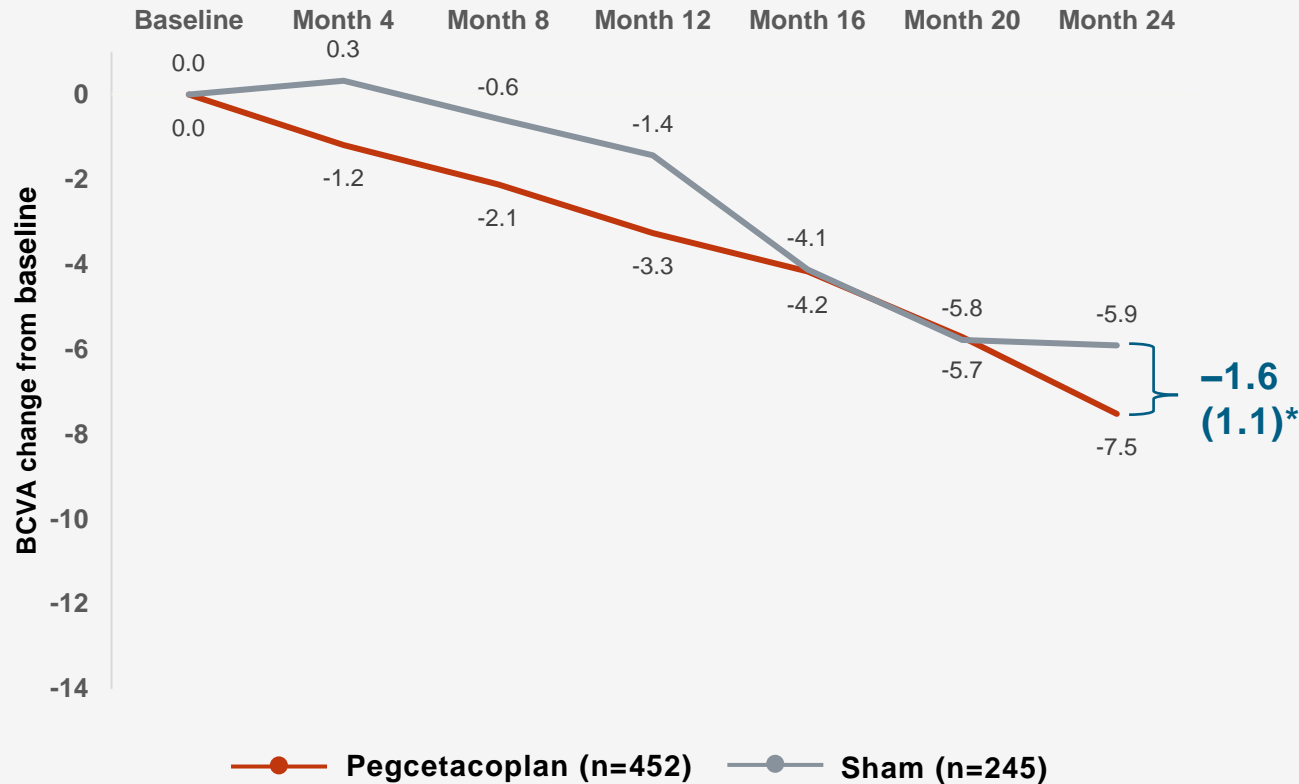
	VFQ-25 composite baseline	VFQ-25 composite change from baseline to Month 24*
PEG	72.0	-6.1
Sham	71.4	-10.2
Difference (SE)		+4.1 (2.4)

*Adjusted difference, mean (SE)
BCVA=best-corrected visual acuity; PEG=pegcetacoplan; SE=standard error; VFQ=visual function questionnaire.

Overall trends in BCVA and VFQ-25 change over time were similar across treated and sham patients with lesions closer to foveal center (<250µm)

Baseline BCVA: PEG 56 and Sham 55 (~20/80 Snellen)

BCVA change from baseline to Month 24



	VFQ-25 composite baseline	VFQ-25 composite change from baseline to Month 24*
PEG	63.8	-4.7
Sham	63.6	-2.4
Difference (SE)		-2.3 (1.0)

*Adjusted difference, mean (SE)
 BCVA=best-corrected visual acuity; PEG=pegcetacoplan; SE=standard error; VFQ=visual function questionnaire.

Conclusions - Subgroup analyses of functional data

- Over 24 months, in patients with lesions further from foveal center:
 - Pegcetacoplan slowed vision loss versus sham (nearly 6 fewer letters lost)
 - Pegcetacoplan-treated patients reported better quality of life than sham-treated patients (4 points higher)
 - A VFQ-25 composite difference of 4–6 points is considered clinically meaningful in neovascular AMD¹

- Limitations
 - RPE-loss data was not available for patients with Cirrus (Zeiss) OCT images
 - Baseline characteristics of patients with Spectralis and Cirrus OCT images were similar
 - *Post hoc* analysis

1. Suñer IJ et al. *Invest Ophthalmol Vis Sci* 2009;50:3629–3629

AMD=age-related macular degeneration; GA=geographic atrophy; OCT=optical coherence tomography; RPE=retinal pigment epithelium; VFQ=visual function questionnaire.

Summary

- 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