Assessment of Geographic Atrophy Lesion Progression in the Phase 3 DERBY and OAKS Trials

Roger A. Goldberg, Michael Singer, Eleonora M. Lad, Renaud Desgraz, Emma Foos, Ramiro Ribeiro, Jean Francois Korobelnik, David Boyer

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Disclosures

- Roger Goldberg has the following financial interests or relationships to disclose:
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  - Equity: Emmetrope Ophthalmics
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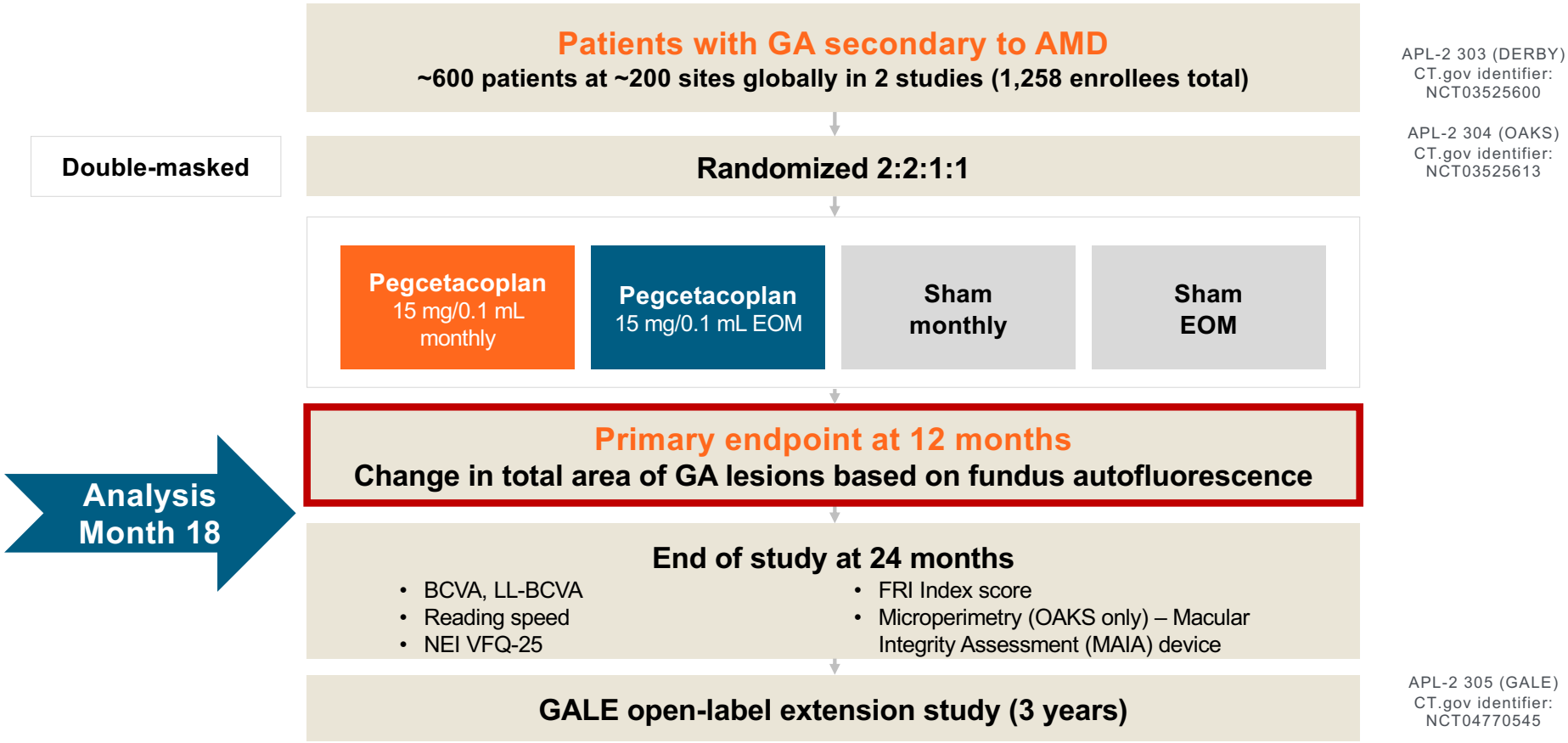
Global Phase 3 program: Design of studies (DERBY & OAKS)



AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; EOM=every other month; FRI=functional reading independence; GA=geographic atrophy; LL=low luminance; NEI VFQ-25=National Eye Institute Visual Function Questionnaire-25.

Key inclusion and exclusion 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 mm^2
  - Foveal and extrafoveal GA allowed
  - If multifocal, at least 1 focal lesion must be ≥1.25 mm^2 (0.5 DA)
  - Presence of perilesional hyperautofluorescence

Key exclusion criteria

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

Ocular history of active CNV in the fellow eye is not exclusionary

AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; DA=disk area; ETDRS=early treatment diabetic retinopathy study; GA=geographic atrophy; RPE=retinal pigment epithelium.

Patient disposition at Month 18

	DERBY			OAKS		
	PM (N=206)	**PEOM (N=208)**	**Sham Pooled (N=207)**	**PM (N=213)**	**PEOM (N=212)**	**Sham Pooled (N=212)**
Completed study through Month 18, n (%)	167 (81.1%)	176 (84.6%)	172 (83.1%)	165 (77.5%)	179 (84.4%)	172 (81.1%)
Discontinued study prior to Month 18, n (%)	39 (18.9%)	32 (15.4%)	35 (16.9%)	48 (22.5%)	33 (15.6%)	40 (18.9%)
Reason for discontinuation, n (%)						
Consent withdrawal	24 (11.7%)	13 (6.3%)	18 (8.7%)	22 (10.3%)	14 (6.6%)	14 (6.6%)
Death	6 (2.9%)	4 (1.9%)	6 (2.9%)	12 (5.6%)	7 (3.3%)	7 (3.3%)
Adverse event	3 (1.5%)	4 (1.9%)	5 (2.4%)	6 (2.8%)	4 (1.9%)	3 (1.4%)
COVID-19 impact	3 (1.5%)	9 (4.3%)	6 (2.9%)	5 (2.3%)	3 (1.4%)	11 (5.2%)
Lost to follow-up	1 (0.5%)	2 (1.0%)	0	3 (1.4%)	4 (1.9%)	4 (1.9%)

These analyses were performed on the Month 18 intent-to-treat (ITT) population. The ITT set includes all randomized patients.
N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Exposure at Month 18

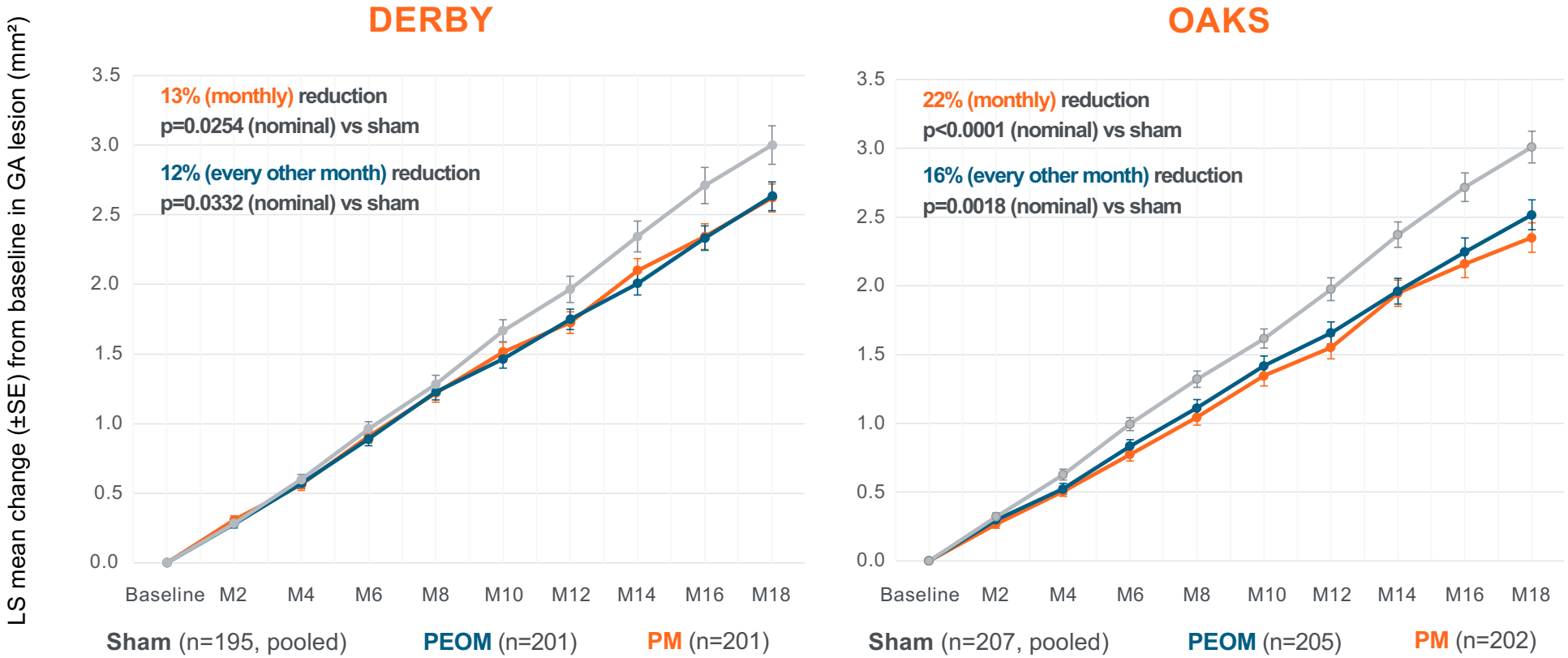
	DERBY			OAKS		
	PM (N=201)	PEOM (N=201)	Sham Pooled (N=195)	PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)
Total number of injections received	2947	1553	2181	2991	1610	2321
Total number of missed injections	418	176	298	359	127	303
Mean number of injections/patient, n (SD)	14.7 (4.03)	7.7 (1.87)	11.2 (4.70)	14.8 (4.08)	7.9 (1.97)	11.2 (4.74)
Mean duration[a] of treatment, days (SD)	482.5 (117.63)	496.1 (105.89)	492.2 (115.21)	485.5 (120.49)	491.1 (120.20)	489.7 (113.78)
Mean compliance, %	87.0%	89.5%	88.8%	88.5%	92.4%	88.6%

The modified intent-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.

[a]Duration of treatment in monthly group is (date of last injection + 30 days) – date of first injection + 1; EOM group is (date of last injection + 60 days) – date of first injection + 1. Duration of treatment is truncated to a patient's early termination date, Month 18 cutoff date, or study completion date, as appropriate. Compliance (%) is the number of injections administered divided by the number of scheduled injections up to completion or discontinuation of study treatment × 100.

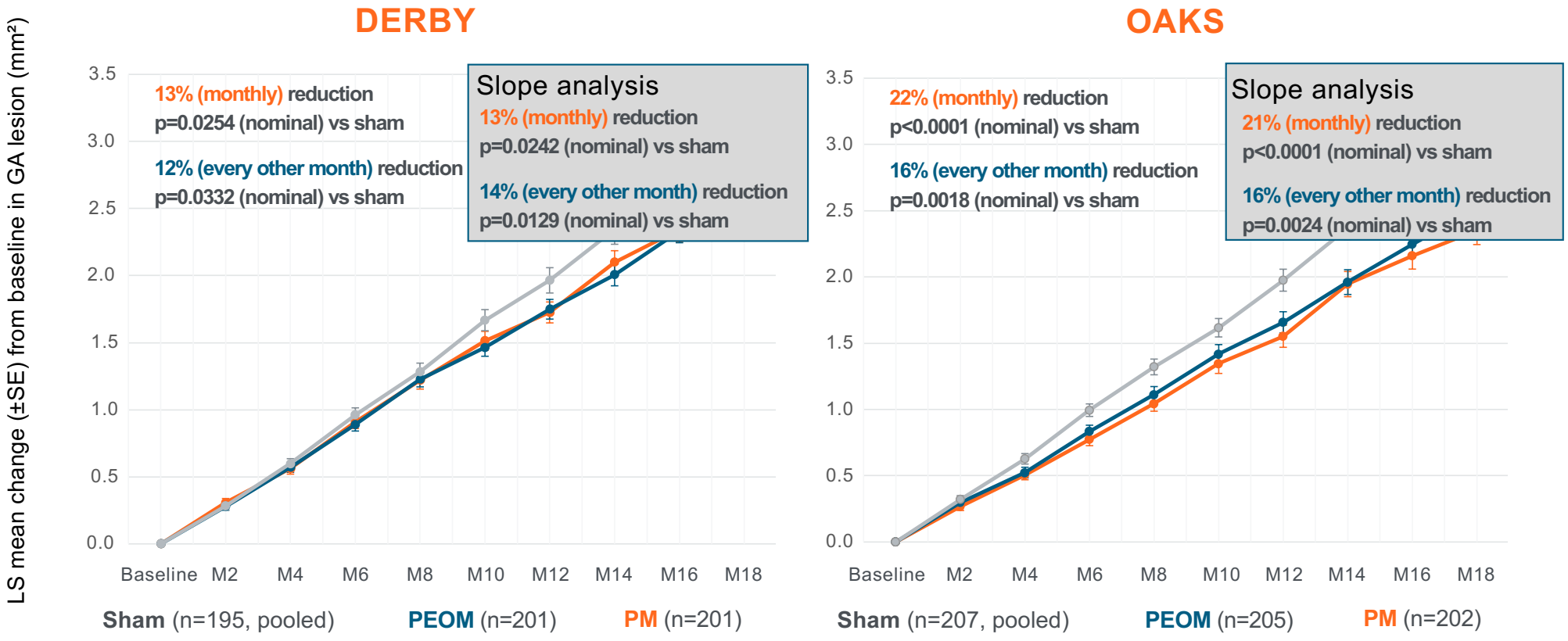
EOM=every other month; GA=geographic atrophy; N=number of patients; PEOM=pegcetacoplan EOM; PM=pegcetacoplan monthly; SD=standard deviation.

Pegcetacoplan reduced GA lesion growth vs sham in **DERBY** and **OAKS** at **Month 18**



LS means estimated from a mixed-effects model for repeated measures. The modified intent-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.
GA=geographic atrophy; LS=least squares; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

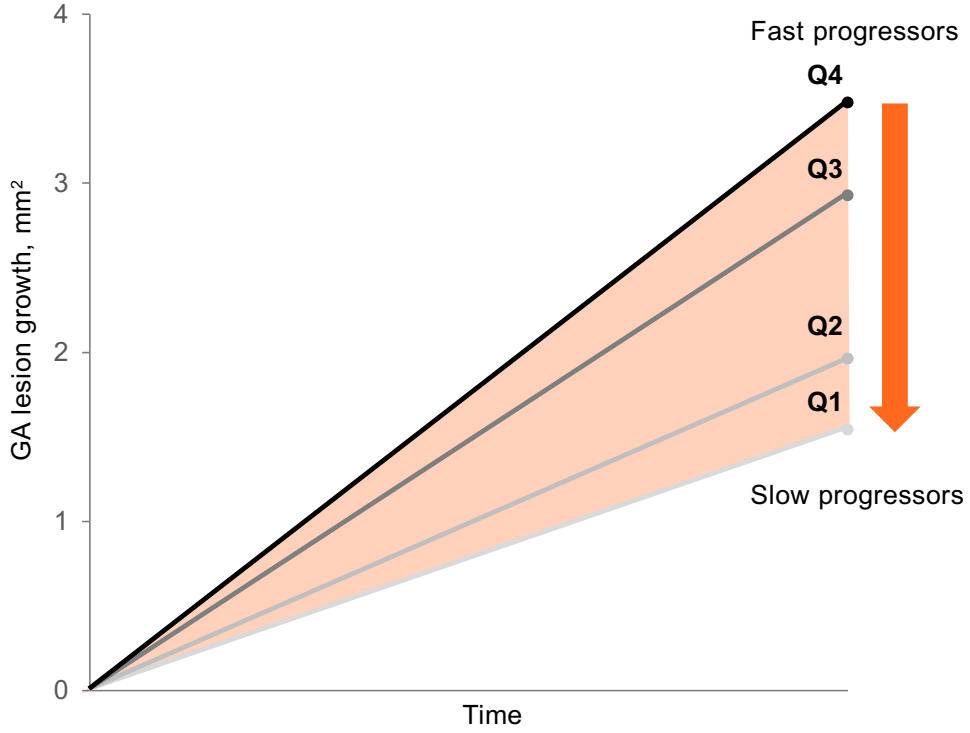
Pegcetacoplan reduced GA lesion growth vs sham in **DERBY** and **OAKS** at **Month 18 – Slope analysis**



Analysis of change from baseline in total area of GA lesions (mm^2) of the study eye with MMRM model assuming a piecewise linear trend in time with knots at month 6 and month 12
PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Post hoc analysis of DERBY and OAKS: Assessment of GA lesion growth over 18 months in quartiles

Schematic representation of progression



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

GA=geographic atrophy; Q1=quartile 1; Q2=quartile 2; Q3=quartile 3; Q4=quartile 4.

Post hoc analysis: Methods and Quartile Definitions

GA progression measured by:

- Change in absolute lesion size from baseline to Month 18

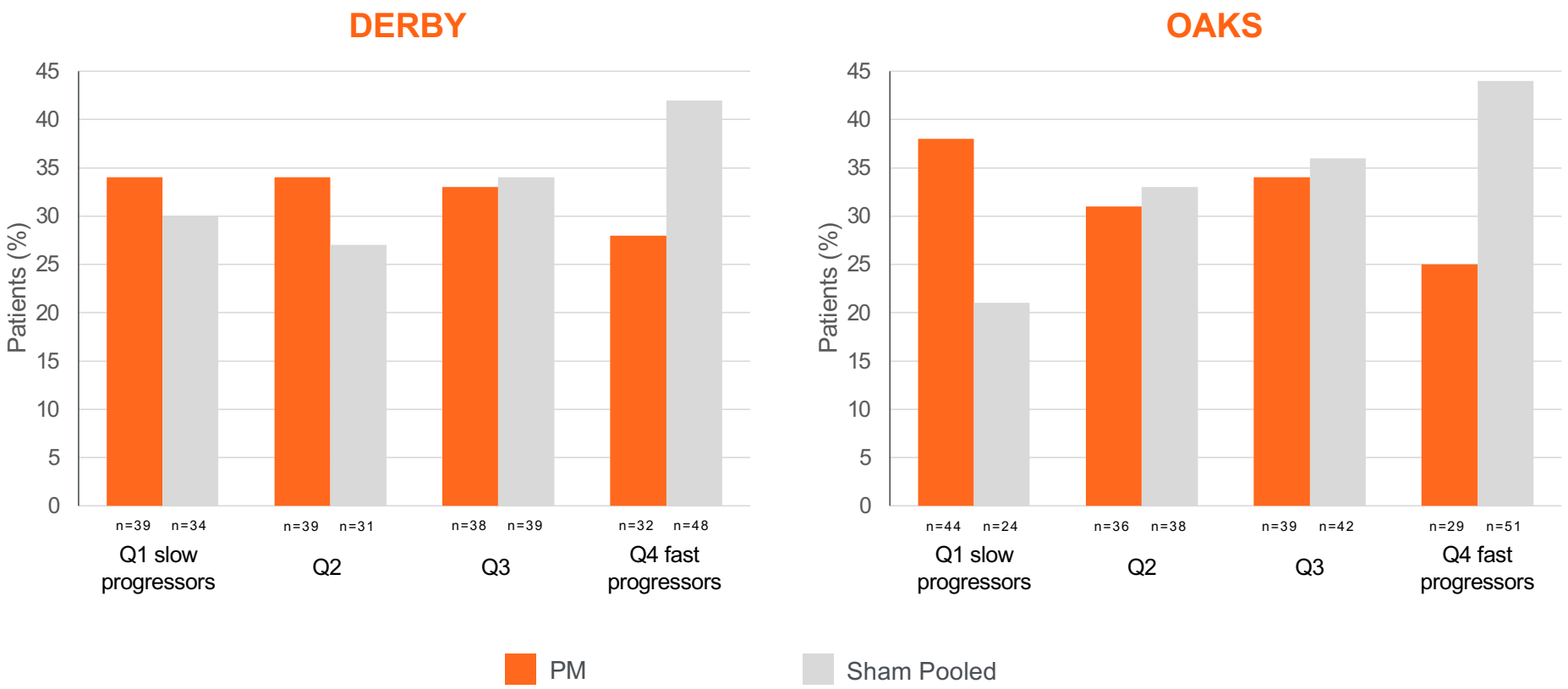
GA progression **by quartiles of growth** assessed in the overall patient population

Patients needed to have a Month 18 lesion growth measurement to be included in the analysis

	DERBY	OAKS
Quartile 1 slowest progressors, mm^2	<1.597 (n=114)	<1.492 (n=116)
Quartile 2 mm^2	≥1.597 – <2.53 (n=114)	≥1.492 – <2.233 (n=116)
Quartile 3 mm^2	≥2.53 – <3.61 (n=114)	≥2.233 – <3.340 (n=116)
Quartile 4 fastest progressors, mm^2	≥3.61 (n=114)	≥3.340 (n=116)

GA=geographic atrophy

Results: Distribution of patients by study arm across quartiles reflects efficacy of pegcetacoplan at 18 months



PM=pegcetacoplan monthly; Q=quartile.

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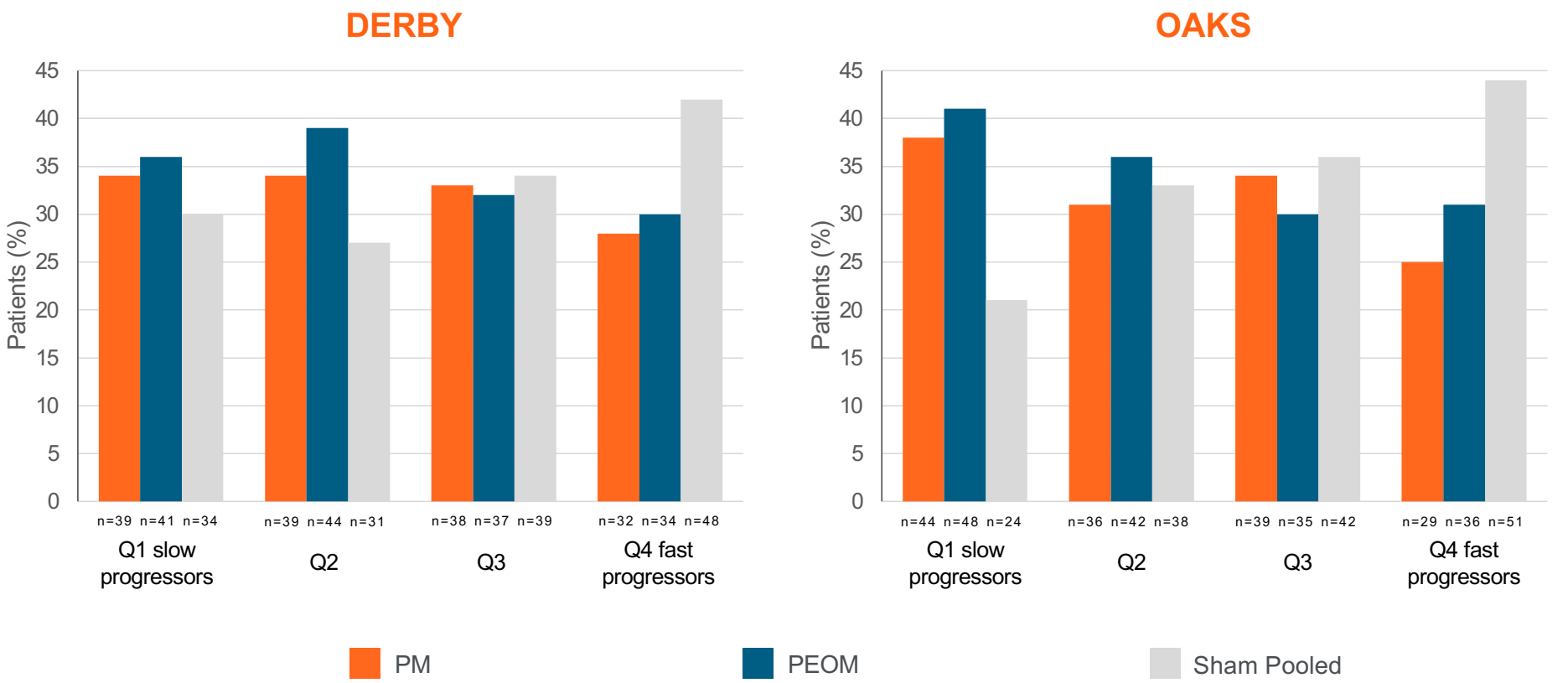

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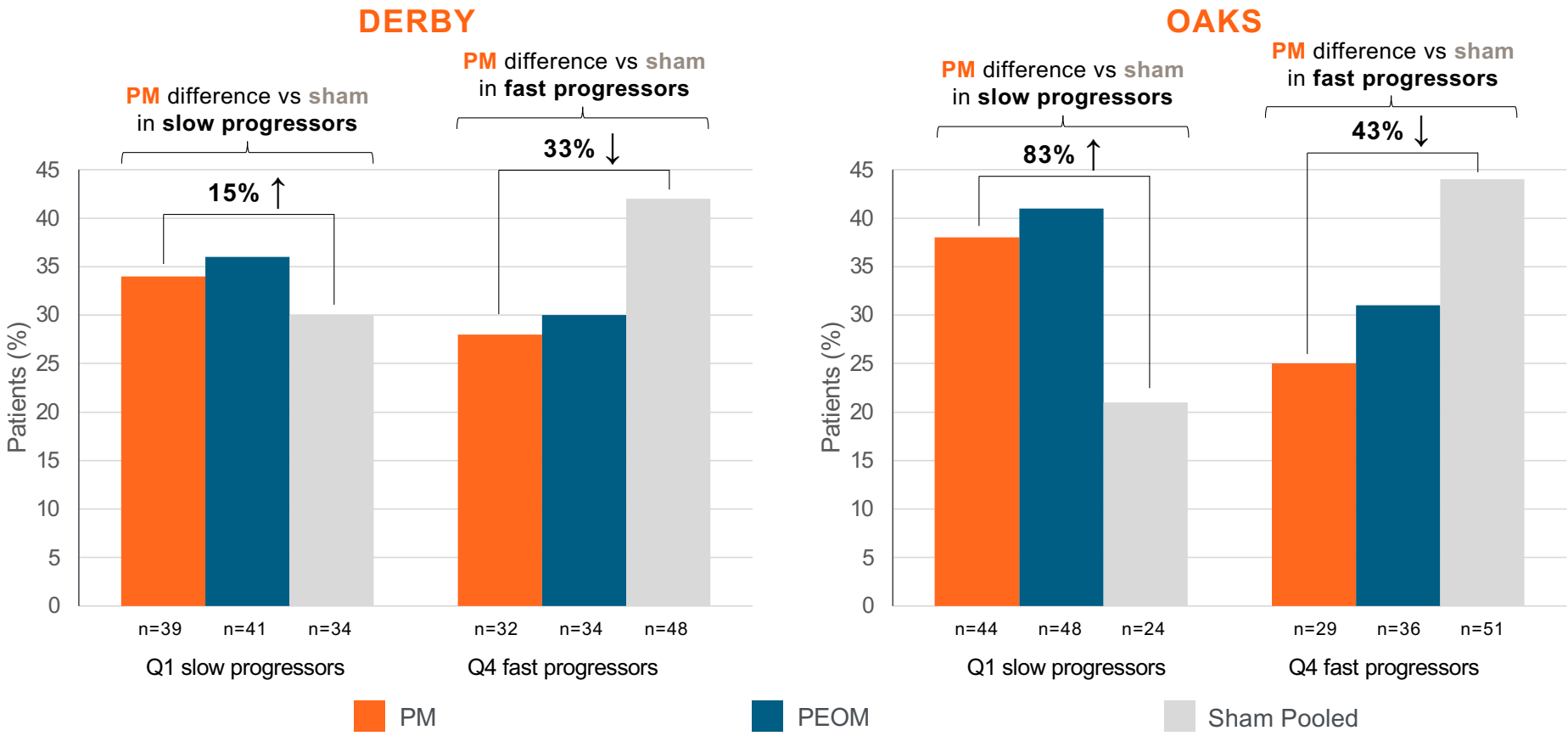

PEOM=pegcetacoplan EOM; PM=pegcetacoplan monthly; Q=quartile.

Relationship of disease characteristics and demographics to GA progression

Factors that have been associated with faster GA progression include:[1–8]

Disease characteristics	Risk of progression
Greater GA lesion size	↑
Presence of Bilateral GA	↑
Greater low luminance deficit	↑
Foveal lesion location	↓
Unifocal lesions	↓
More Intermediate/large drusen	↓

Demographic risk factors

Increasing age, male sex, white ethnicity, hypertension, diabetes, smoking, family history of AMD, BMI

BMI=body mass index; GA=geographic atrophy.

1. Sunness JS et al. *Ophthalmology* 1999;106:1768-79; 2. Grassmann F et al. *Eur J Pharm Biopharm* 2015;95:194-202; 3. Fleckenstein M et al. *Invest Ophthalmol Vis Sci* 2011;52:3761–6; 4. Fleckenstein M et al. *Invest Ophthalmol Vis Sci* 2010;51:3846-52; 5. Schmitz-Valckenberg S et al. *Ophthalmology* 2016;123:361–8; 6. Schmitz-Valckenberg S et al. *Invest Ophthalmol Vis Sci* 2011;52:5009–15; 7. Folgar FA et al. *Ophthalmology* 2016;123:39–50; 8. Sunness JS et al. *Ophthalmology* 2008;115:1480–8.

DERBY (sham): Relationship of baseline characteristics to speed of progression

DERBY (sham pooled arm)

	Risk of progression	Slowest progressors n=34	Fastest progressors n=48
GA lesion size (mean, mm^2)	↑	5.6	10.2
Bilateral GA (%)	↑	68%	85%
Mean low luminance deficit (ETDRS letters)	↑	20	32
Foveal lesion location (%)	↓	79%	44%
Unifocal lesions (%)	↓	35%	27%
Intermediate/large drusen >20 (%)	↓	74%	27%

↑ Associated with faster progression

↓ Associated with slower progression

GA=geographic atrophy; CNV=choroidal neovascularization; ETDRS=early treatment diabetic retinopathy study.

OAKS (sham): Relationship of baseline characteristics to speed of progression

OAKS (sham pooled arm)

	Risk of progression	Slowest progressors n=24	Fastest progressors n=51
GA lesion size (mean, mm^2)	↑	5.5	9.8
Bilateral GA (%)	↑	63%	86%
Mean low luminance deficit (ETDRS letters)	↑	15	29
Foveal lesion location (%)	↓	88%	55%
Unifocal lesions (%)	↓	46%	22%
Intermediate/large drusen >20 (%)	↓	71%	33%

↑ Associated with faster progression

↓ Associated with slower progression

GA=geographic atrophy; CNV=choroidal neovascularization; ETDRS=early treatment diabetic retinopathy study.

Conclusions

- Pegcetacoplan treatment was associated with a higher percentage of patients in the PM and PEOM arms in the slower progressing quartiles when compared with sham
- The findings support the effect of pegcetacoplan in reducing GA disease progression and provides additional insights on factors that may impact lesion growth
- The relationship between key GA disease characteristics and GA progression is consistent with findings in the literature and highlights the broad, representative nature of the DERBY and OAKS study population

GA=geographic atrophy; PEOM=pegcetacoplan EOM; PM=pegcetacoplan monthly