Efficacy of Pegcetacoplan in Subgroups Defined by Distance from the Foveal Center Point in the Phase 3 OAKS and DERBY studies of Patients with Geographic Atrophy

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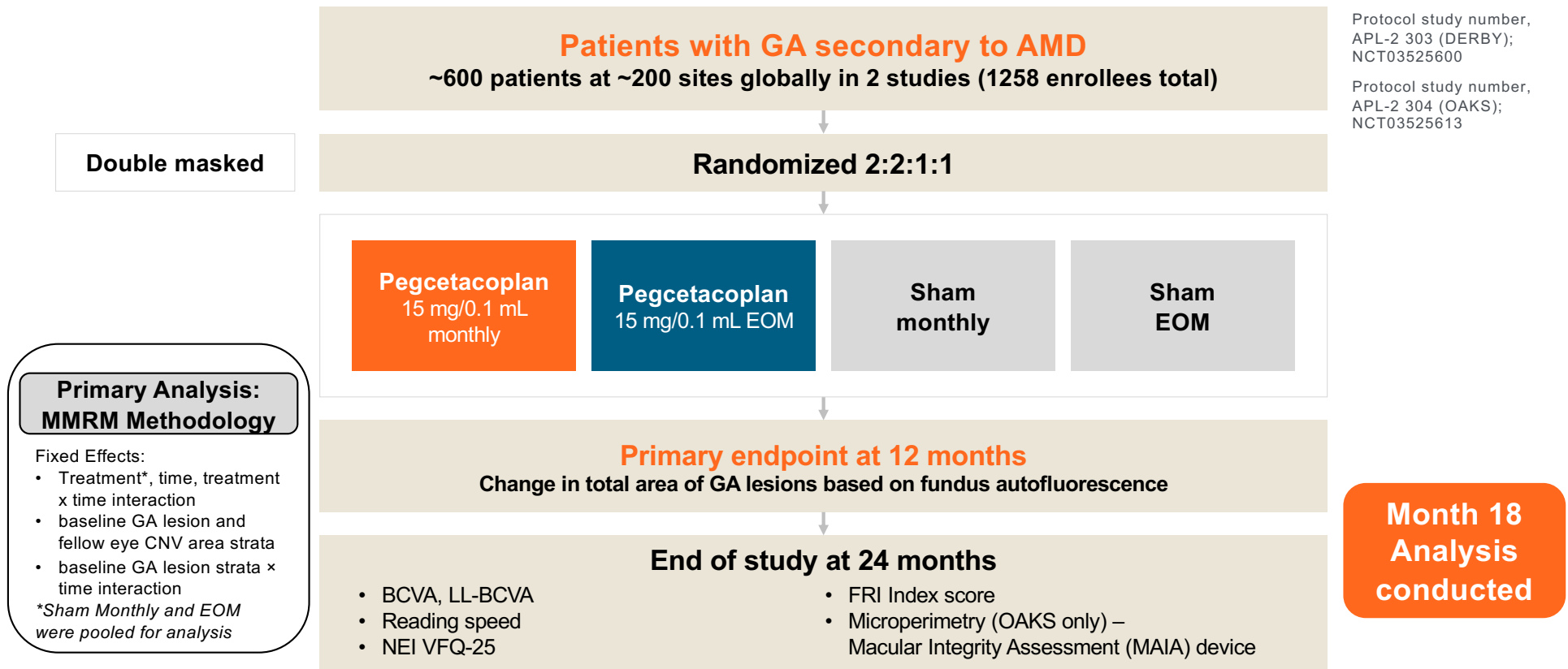The Macula Society 45th Annual Meeting, Berlin, Germany

Disclosures

- Frank G. Holz has the following financial interests or relationships to disclose:

  - Consulting: Acucela, Alcon, Apellis, Bayer, Boehringer-Ingelheim, Genentech/Roche, Grayburg Vision, Heidelberg Engineering, ivericBio, Lin Bioscience, Novartis, Oxurion, Pixium Vision, Stealth Biotherapeutics, Zeiss

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Introduction

- Natural history data, supported by data from the sham arms of the Phase 3 studies of pegcetacoplan in GA, indicate that rate of GA lesion growth varies with distance to the foveal center point

  - More rapid growth observed in lesions not involving the center point of the fovea

- Therapeutic efficacy of C3 inhibition with pegcetacoplan at 12 months was observed to be greater in lesions not involving the center point of the fovea at baseline

  - Efficacy remained robust in these lesions at the 18-month analysis

  - In lesions involving the center of the fovea, treatment effect appeared to increase with longer follow-up

  - Majority of patients in DERBY and OAKS had lesions involving the foveal center point (62% in DERBY, 64% in OAKS month 18 mITT set)

GA=geographic atrophy; mITT=modified intent-to-treat.

Global phase 3 program: Design of studies

Patients with GA secondary to AMD
~600 patients at ~200 sites globally in 2 studies (1258 enrollees total)

Protocol study number, APL-2 303 (DERBY); NCT03525600

Protocol study number, APL-2 304 (OAKS); NCT03525613

Double masked

Randomized 2:2:1:1

Pegcetacoplan 15 mg/0.1 mL monthly	Pegcetacoplan 15 mg/0.1 mL EOM	Sham monthly	Sham EOM

Primary Analysis: MMRM Methodology

Fixed Effects:
- Treatment*, time, treatment x time interaction
- baseline GA lesion and fellow eye CNV area strata
- baseline GA lesion strata × time interaction

Sham Monthly and EOM were pooled for analysis

Primary endpoint at 12 months
Change in total area of GA lesions based on fundus autofluorescence

Month 18 Analysis conducted

End of study at 24 months

- BCVA, LL-BCVA
- Reading speed
- NEI VFQ-25

- FRI Index score
- Microperimetry (OAKS only) – Macular Integrity Assessment (MAIA) device

AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CNV=choroidal neovascularization; EOM=every other month; FRI=functional reading index; GA=geographic atrophy; LL=low luminance; MMRM=mixed-effect model for repeated measures; NEI-VFQ=National Eye Institute Visual Function Questionnaire-25.

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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 exudative AMD in the study eye, including presence of RPE tear (assessed by reading center)

Ocular history of CNV in the fellow eye is not exclusionary

AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CNV=choroidal neovascularization; DA=disk areas; ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; RPE=retinal pigment epithelium.

Patient disposition at Month 18

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

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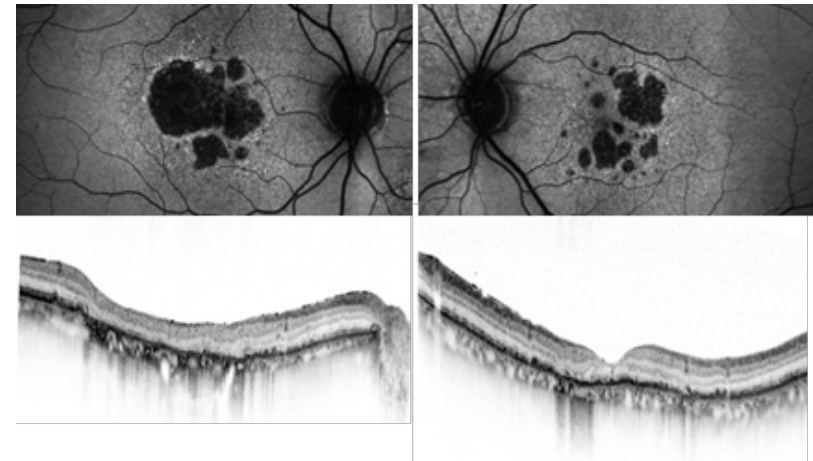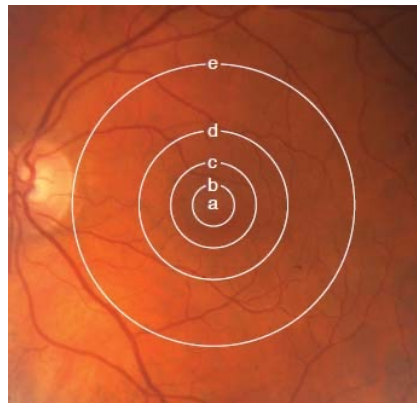PM=pegcetacoplan monthly; PEOM=pegcetacoplan every other month.

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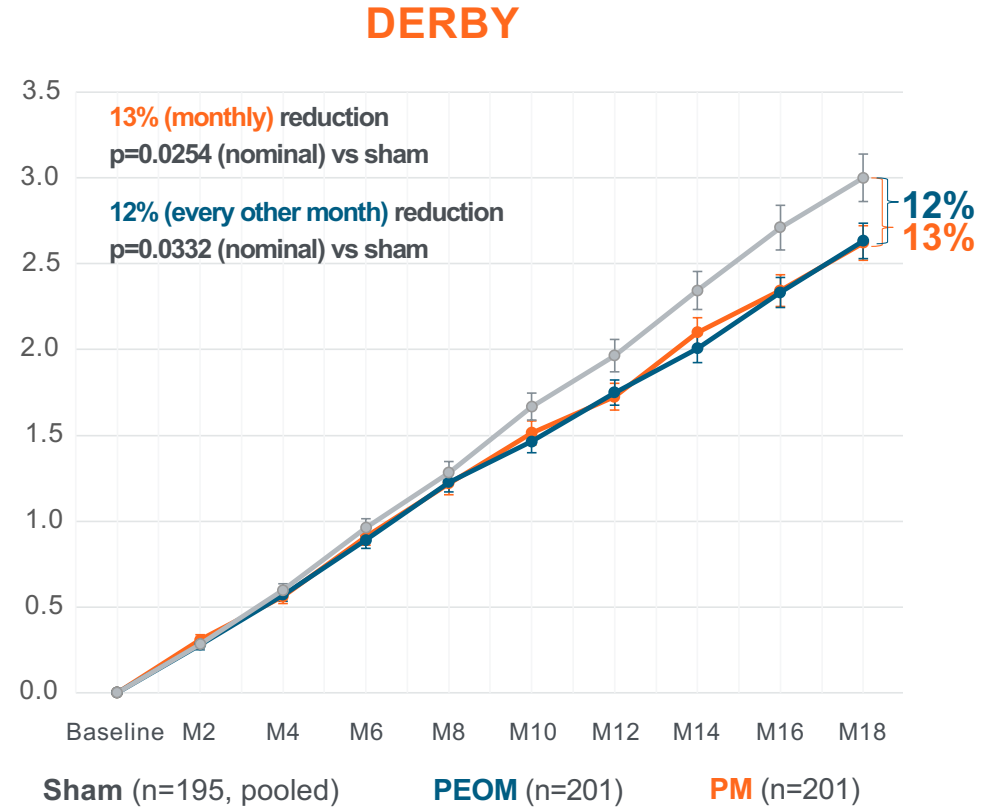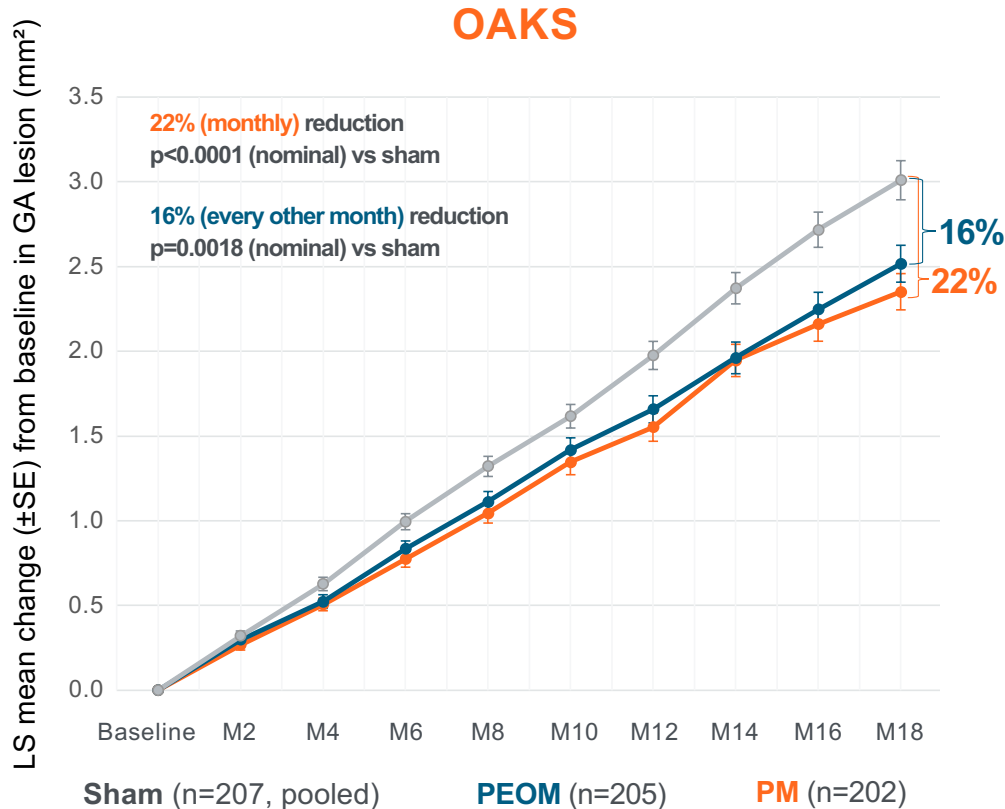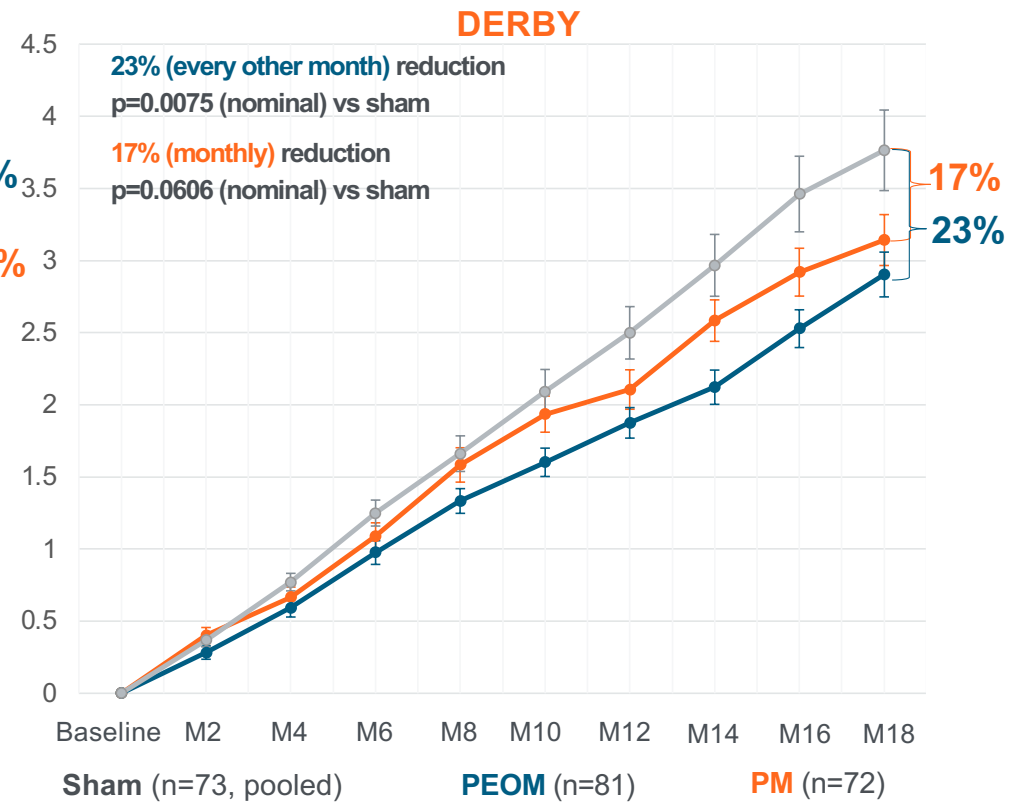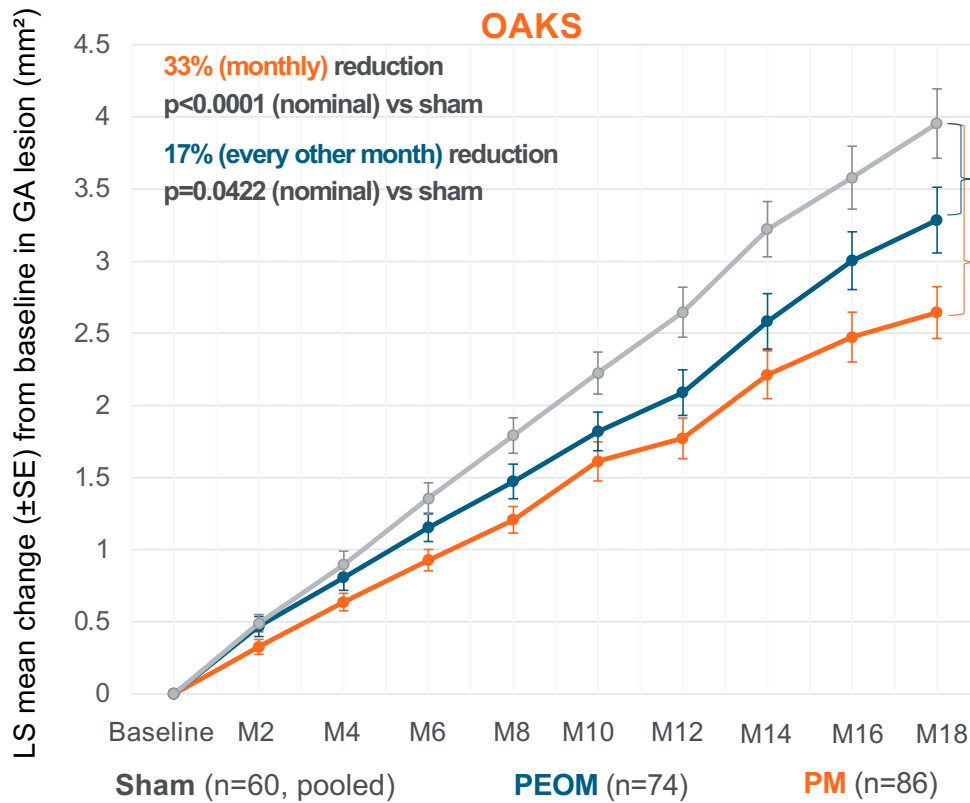

LS means estimated from a mixed-effects model for repeated measures (MMRM). The modified intent-to-treat population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion area in the study eye.
M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

DERBY/OAKS methodology and definitions for original extrafoveal/foveal subgroup analysis

- During FAF lesion size grading, two masked graders also assessed lesion location
  - Each grader located the center point of the fovea using FAF and OCT (if needed)
  - If there was GA present, as identified on (FAF and OCT), at the center point of the fovea, the subject was classified as having *subfoveal involvement*
  - If the <u>center point</u> *did not* have GA, the grader measured the distance to the nearest GA border
    - **These eyes were classified as *extrafoveal* in the original analysis, regardless of the distance to GA border**
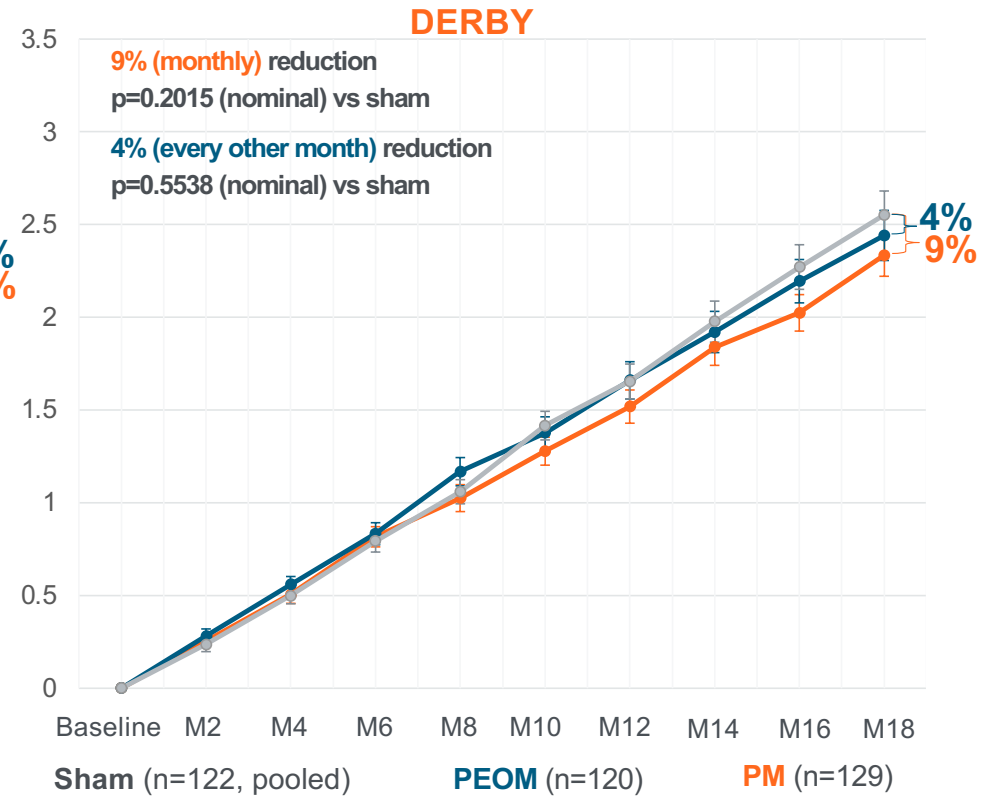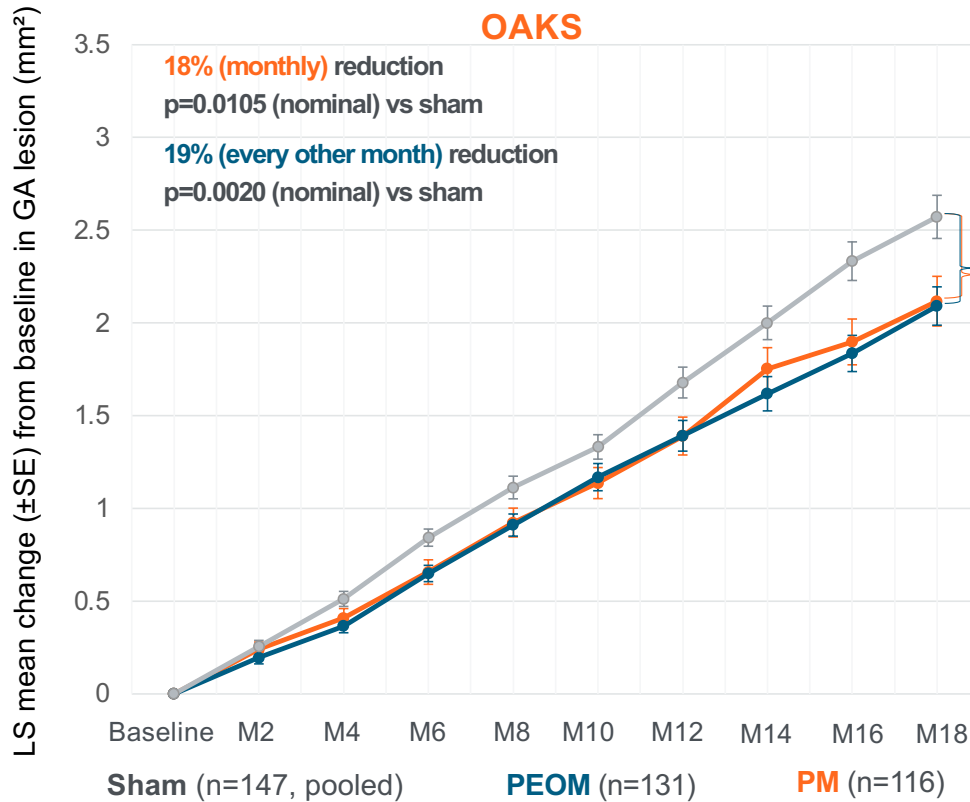 - Intergrader agreement for distance to lesion border was excellent

GA=geographic atrophy; FAF=fundus autofluorescence; OCT=optical coherence tomography.

Pegcetacoplan continued to show reduced lesion growth in patients with **extrafoveal lesions** at **Month 18**

OAKS

33% (monthly) reduction
p<0.0001 (nominal) vs sham

17% (every other month) reduction
p=0.0422 (nominal) vs sham

17%
33%

Sham (n=60, pooled)   PEOM (n=74)   PM (n=86)

DERBY

23% (every other month) reduction
p=0.0075 (nominal) vs sham

17% (monthly) reduction
p=0.0606 (nominal) vs sham

17%
23%

Sham (n=73, pooled)   PEOM (n=81)   PM (n=72)

LS mean change (±SE) from baseline in GA lesion (mm^2)
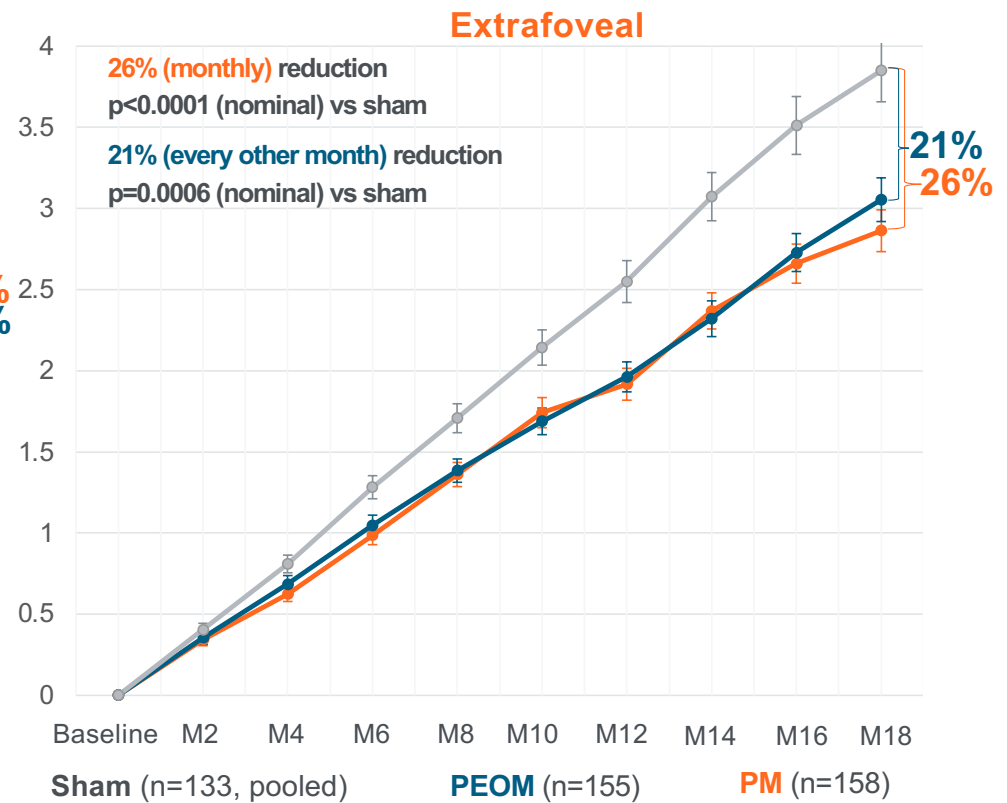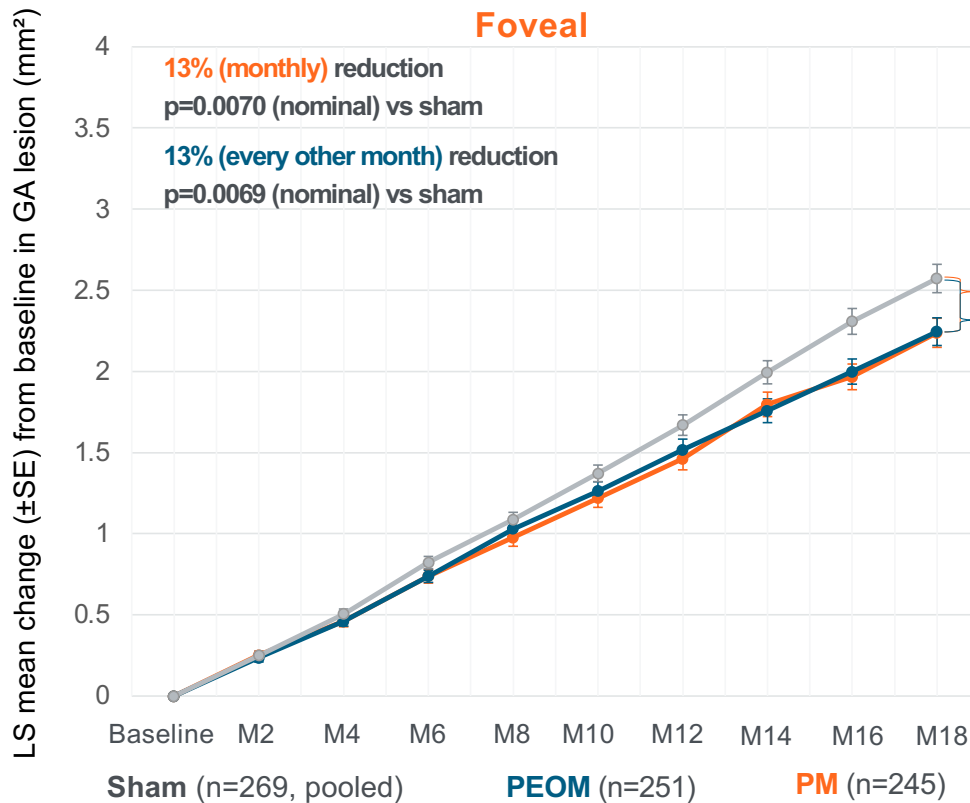
Baseline M2 M4 M6 M8 M10 M12 M14 M16 M18

Extrafoveal is defined as lesion with distance >0 to foveal center point. LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis. LS=least square; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

In OAKS, pegcetacoplan reduced lesion growth in patients with **foveal** lesions at **Month 18**

OAKS

18% (monthly) reduction
p=0.0105 (nominal) vs sham

19% (every other month) reduction
p=0.0020 (nominal) vs sham

19%
18%

DERBY

9% (monthly) reduction
p=0.2015 (nominal) vs sham

4% (every other month) reduction
p=0.5538 (nominal) vs sham

4%
9%

LS mean change (±SE) from baseline in GA lesion (mm²)

Baseline M2 M4 M6 M8 M10 M12 M14 M16 M18

Sham (n=147, pooled)   **PEOM** (n=131)   **PM** (n=116)

Sham (n=122, pooled)   **PEOM** (n=120)   **PM** (n=129)

Foveal was defined as lesion edge within center point of the fovea. LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis. LS=least square; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

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In the combined analysis, pegcetacoplan reduced **foveal** and **extrafoveal lesion** growth at **Month 18**

Foveal

13% (monthly) reduction
p=0.0070 (nominal) vs sham

13% (every other month) reduction
p=0.0069 (nominal) vs sham

13%
13%

Extrafoveal

26% (monthly) reduction
p<0.0001 (nominal) vs sham

21% (every other month) reduction
p=0.0006 (nominal) vs sham

21%
26%

LS mean change (±SE) from baseline in GA lesion (mm²)

Baseline M2 M4 M6 M8 M10 M12 M14 M16 M18

Sham (n=269, pooled) **PEOM** (n=251) **PM** (n=245)

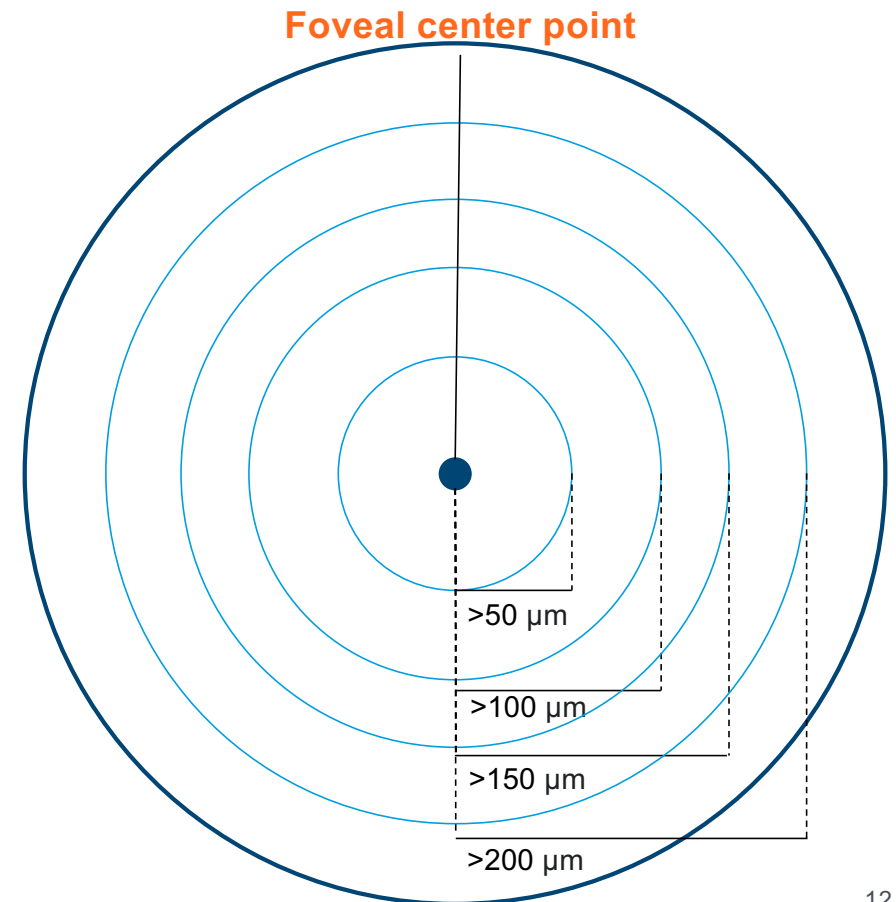**Sham** (n=133, pooled) **PEOM** (n=155) **PM** (n=158)

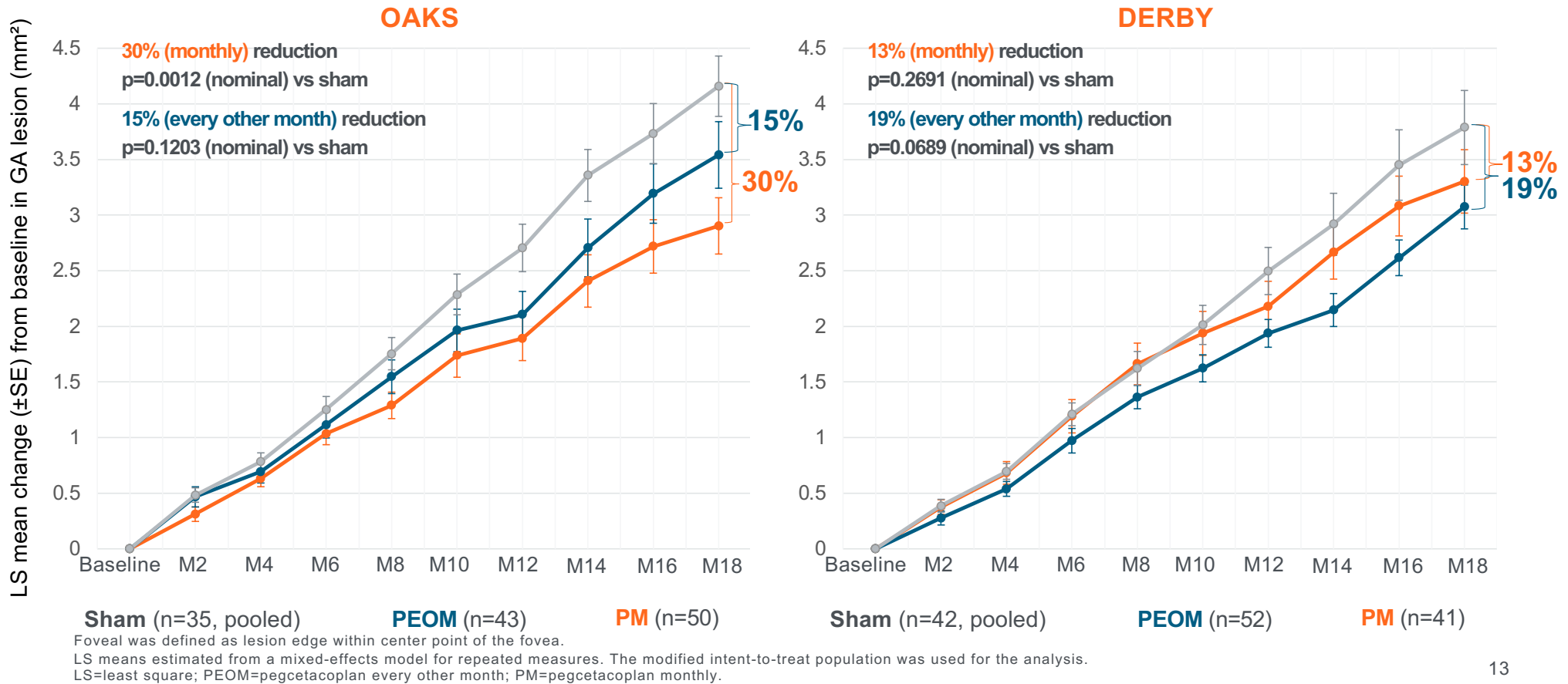Foveal was defined as lesion edge within center point of the fovea.
LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis.
LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

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Additional subgroup analyses based on lesion distance from foveal center point
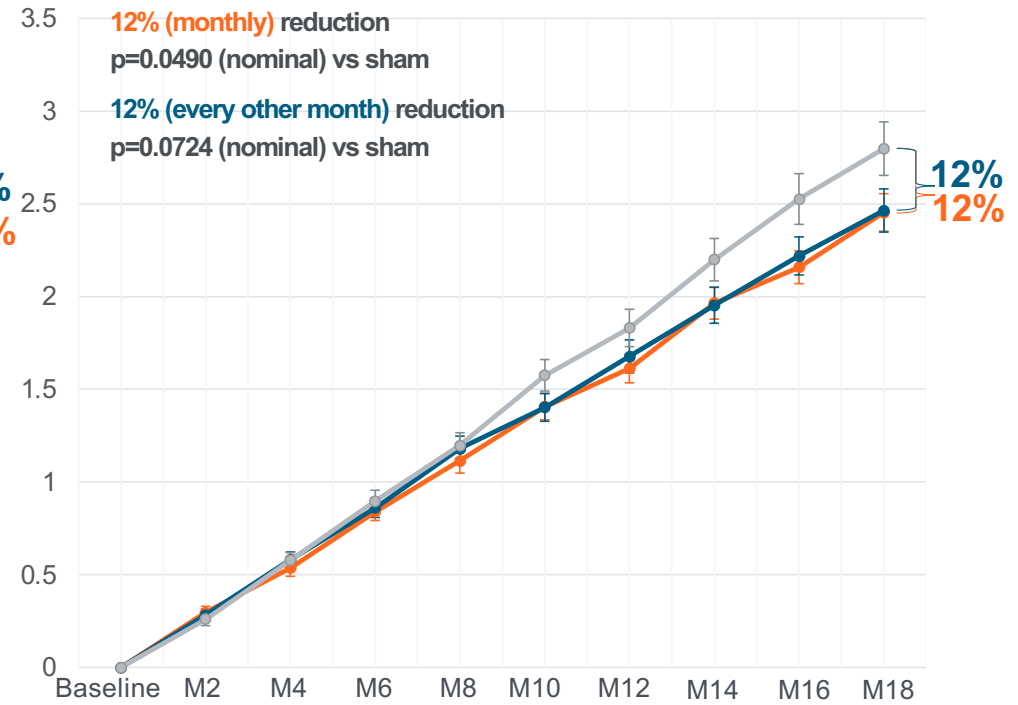
- To build on these previous analyses of patient subgroups defined by lesion distance >0 microns versus =0 microns to the foveal center point, this analysis was repeated using the following cutoff from the foveal center point:
  - ≤ 250 microns
  - > 250 microns
- Additional subgroups have been analyzed to explore the relationship between distance to foveal center point and treatment effect
  - > 50 microns
  - >100 microns
  - >150 microns
  - >200 microns

Foveal center point

>50 µm

>100 µm

>150 µm

>200 µm

OAKS and DERBY: Distance to foveal center point in study eye >250 microns

OAKS

30% (monthly) reduction
p=0.0012 (nominal) vs sham

15% (every other month) reduction
p=0.1203 (nominal) vs sham

15%
30%

DERBY

13% (monthly) reduction
p=0.2691 (nominal) vs sham

19% (every other month) reduction
p=0.0689 (nominal) vs sham

13%
19%

LS mean change (±SE) from baseline in GA lesion (mm²)

Sham (n=35, pooled)   PEOM (n=43)   PM (n=50)

Sham (n=42, pooled)   PEOM (n=52)   PM (n=41)

Foveal was defined as lesion edge within center point of the fovea.
LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis.
LS=least square; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

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OAKS and DERBY: Distance to foveal center point in study eye ≤250 microns

Left panel:
- 22% (monthly) reduction p=0.0002 (nominal) vs sham
- 19% (every other month) reduction p=0.0008 (nominal) vs sham

19%
22%

Sham (n=172, pooled)   PEOM (n=162)   PM (n=152)

Right panel:
- 12% (monthly) reduction p=0.0490 (nominal) vs sham
- 12% (every other month) reduction p=0.0724 (nominal) vs sham

12%
12%

Sham (n=153, pooled)   PEOM (n=149)   PM (n=160)

Y-axis: LS mean change (±SE) from baseline in GA lesion (mm²)
X-axis: Baseline, M2, M4, M6, M8, M10, M12, M14, M16, M18

Foveal was defined as lesion edge within center point of the fovea.
LS means estimated from a mixed-effects model for repeated measures. The modified intent-to-treat population was used for the analysis.
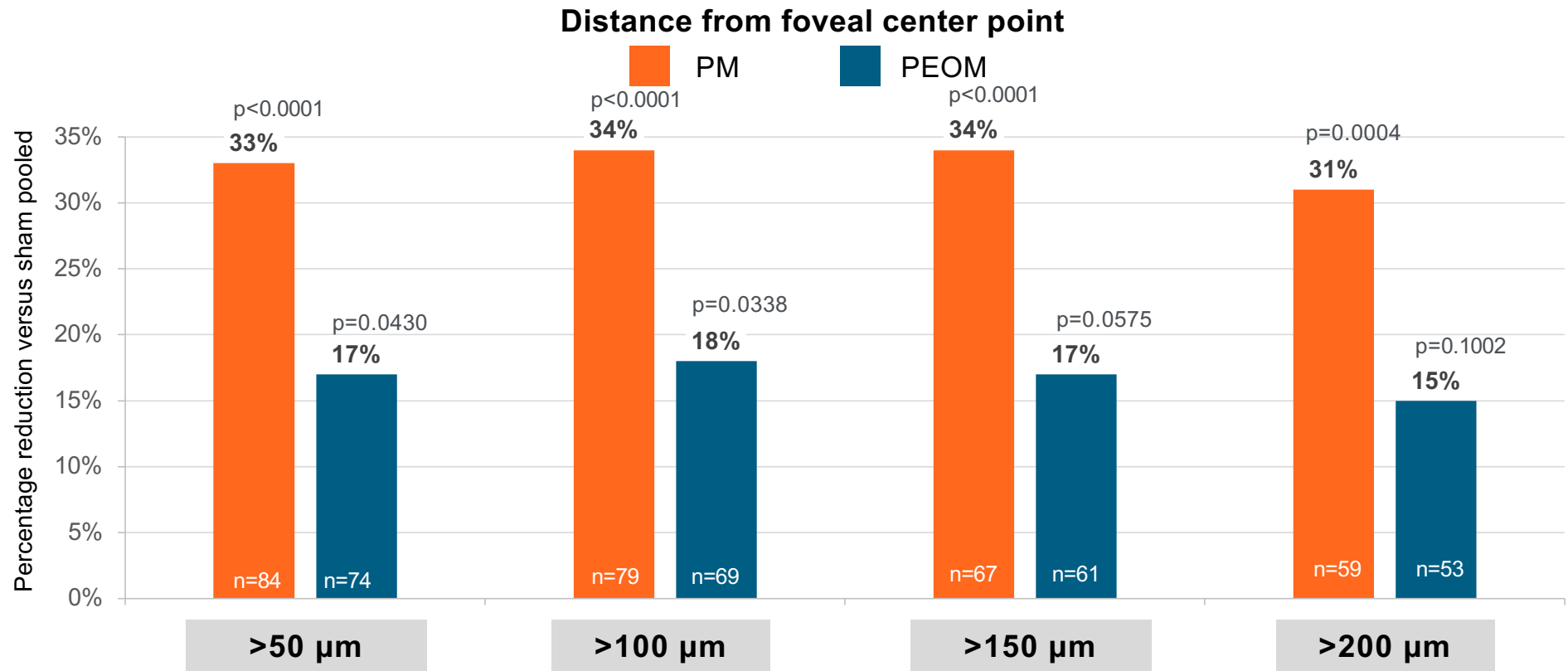LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

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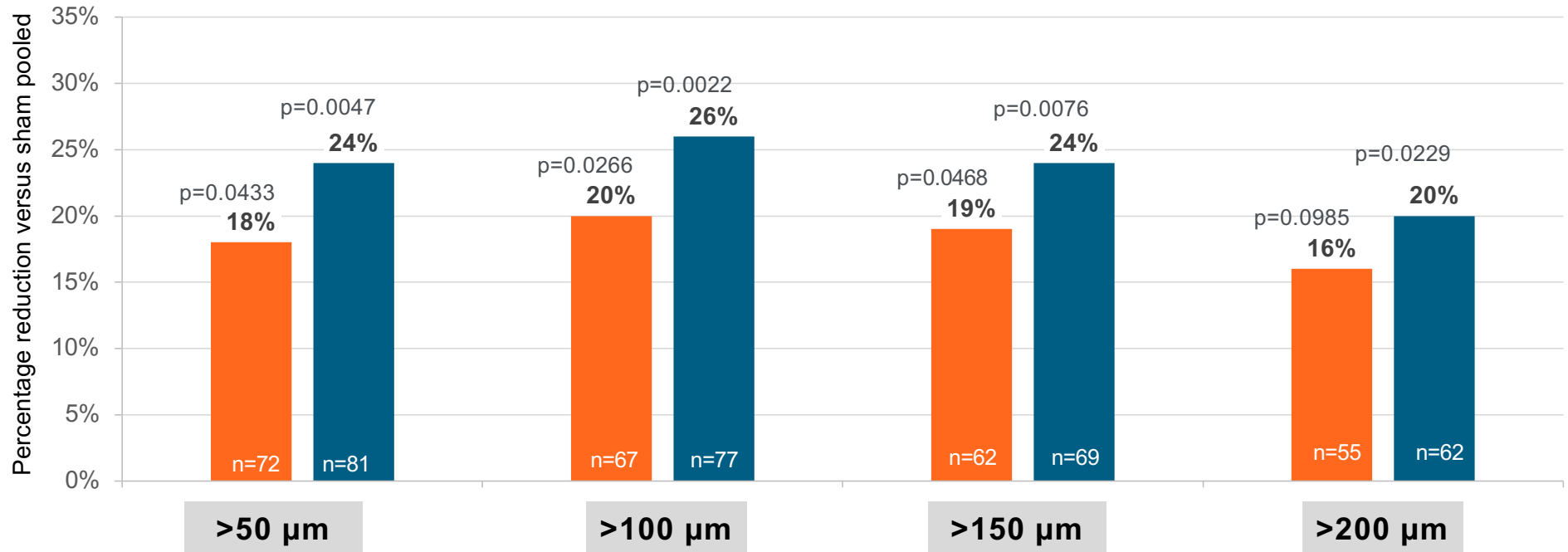# OAKS: Consistent efficacy with increasing distance from foveal center point

LS means estimated from a mixed-effects model for repeated measures. All p-values are nominal.
LS=least square; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

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DERBY: Consistent efficacy with increasing distance from foveal center point

Distance from foveal center point

- PM
- PEOM

Percentage reduction versus sham pooled

>50 μm
- p=0.0433, **18%**, n=72 (PM)
- p=0.0047, **24%**, n=81 (PEOM)

>100 μm
- p=0.0266, **20%**, n=67 (PM)
- p=0.0022, **26%**, n=77 (PEOM)

>150 μm
- p=0.0468, **19%**, n=62 (PM)
- p=0.0076, **24%**, n=69 (PEOM)

>200 μm
- p=0.0985, **16%**, n=55 (PM)
- p=0.0229, **20%**, n=62 (PEOM)

LS means estimated from a mixed-effects model for repeated measures. All p-values are nominal.
PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Conclusions

- Pegcetacoplan administered monthly or every other month demonstrated sustained reductions in GA lesion growth over 18 months across subgroups defined by different distances to the foveal center point

- While efficacy tended to be stronger in lesions not contacting the foveal center point, pegcetacoplan demonstrated reduction in lesion growth vs sham regardless of distance from the fovea

- Topographic differences of the RPE/neurosensory retinal tissue and local complement activity may underlie differences in lesion growth and therapeutic efficacy

RPE: retinal pigment epithelium.