Efficacy of intravitreal pegcetacoplan in geographic atrophy: results from the DERBY and OAKS trials

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Disclosures

- Dr. Heier is a consultant for 4DMT, Adverum, Aerie, Aerpio, Aldeyra, Allegro, Alzheon, Annexon, Apellis, Aprea, Asclepix, Aviceda, BVT, Dark Horse, DTx, Eloxx, Galimedix, Genentech, Graybug, Gyroscope, Iveric Bio, jCyte, Kanghong, LensGen, NGM, Novartis, Ocular Therapeutix, OcuTerra, Oxurion, Palatin, Regeneron, Regenxbio, Stealth, Thea, Version, Vinci, and Voyant.
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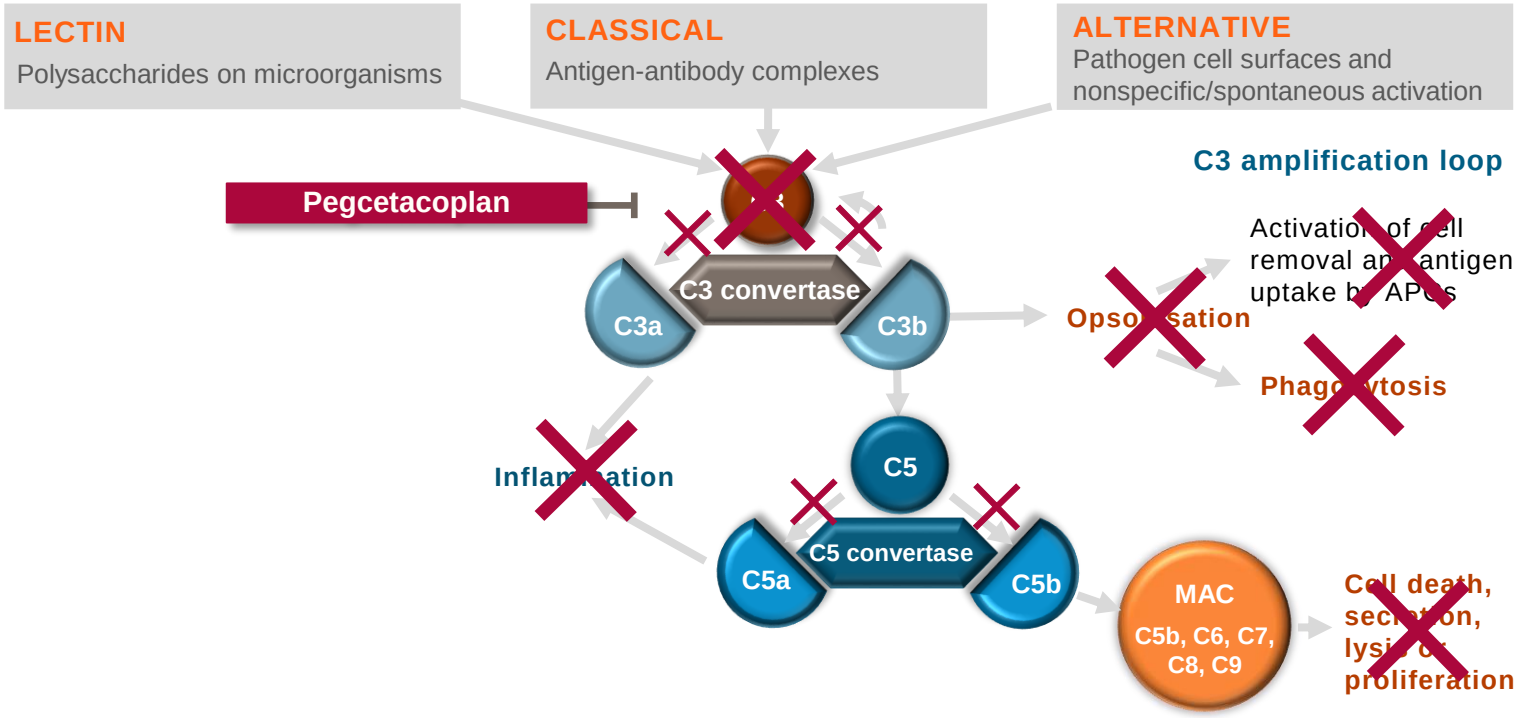
Introduction

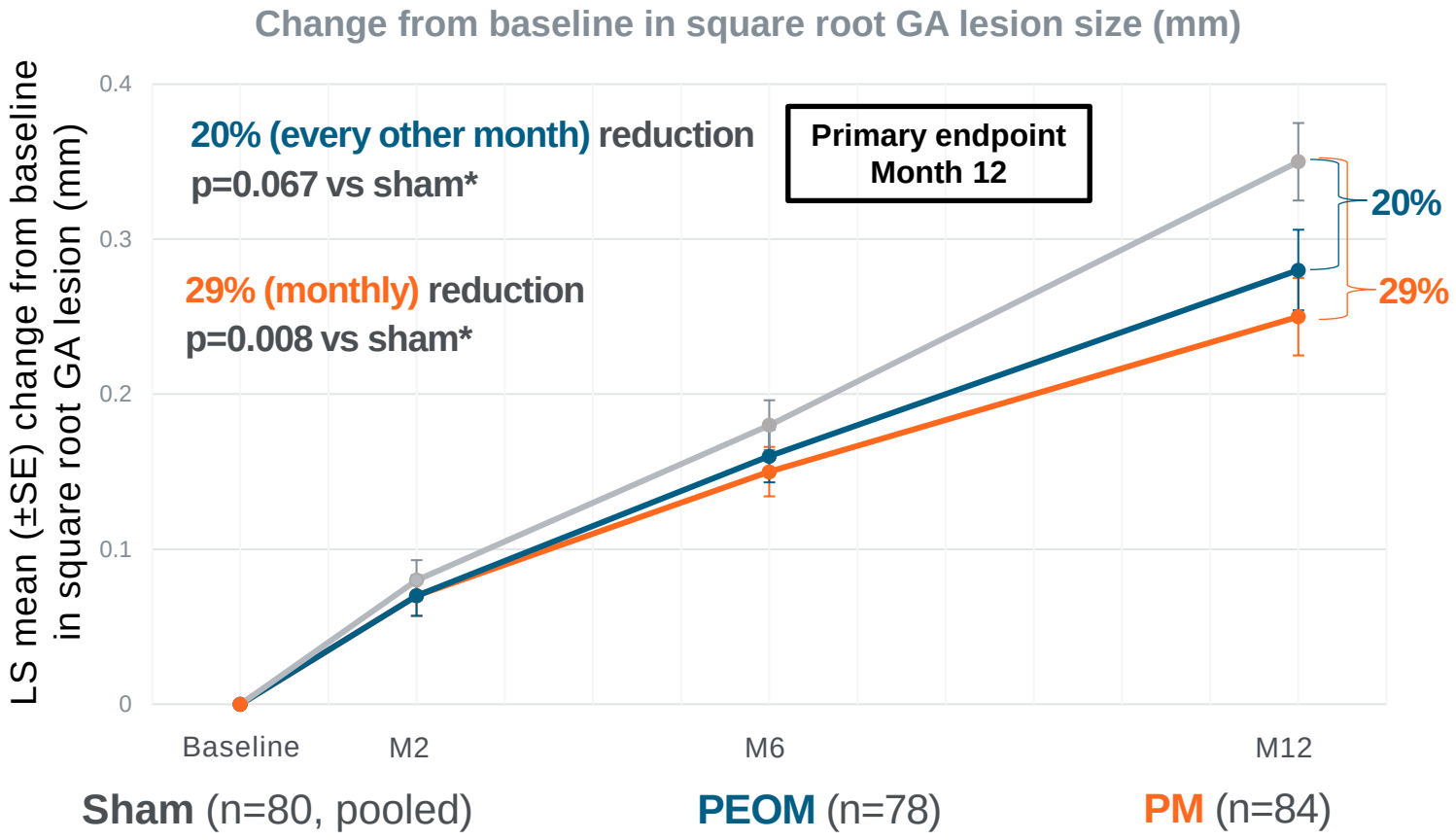


- Dysregulation of the complement cascade has been implicated in GA pathogenesis
- All 3 complement pathways end in the central cleavage of C3
- Pegcetacoplan is a pegylated, highly-selective peptide that binds C3, preventing its cleavage
- Inhibition of C3 blocks steps in the complement cascade needed for opsonization, inflammation, and formation of MAC

Figure adapted from Ricklin D, et al. *Immunol Rev* 2016;274(1):33-58.
APC=antigen-presenting cell; GA=geographic atrophy; MAC=membrane attack complex.
Liao DS, et al. Ophthalmology 2020;127:186–95.

Introduction and objective

Phase 2 FILLY Results



- **Phase 3 DERBY & OAKS objective:** to assess the efficacy and safety of multiple intravitreal injections of pegcetacoplan in patients with GA secondary to AMD

*P<0.1 was the predefined threshold for statistical significance in FILLY.
AMD=age-related macular degeneration; GA=geographic atrophy; LS=least squares; M=Month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.
Liao DS, et al. Ophthalmology 2020;127:186–95.

Global phase 3 program: Design of studies

Double masked

Patients with GA secondary to AMD

~600 patients at ~200 sites globally in 2 studies (1258 enrollees total)

↓

Randomized 2:2:1:1

↓

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

↓

Primary endpoint at 12 months

Change in total area of GA lesions based on fundus autofluorescence

↓

End of study at 24 months

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

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

AMD=age-related macular degeneration; EOM=every other month; GA=geographic atrophy.

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 neovascularisation; DA=disc area; ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; RPE=retinal pigment epithelium.

Key endpoints

Primary

- Change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF

Secondary (prespecified analyses to be conducted at 24 months)

- BCVA, LL-BCVA, low-luminance deficit
- Reading speed
- Microperimetry (OAKS study only*) — Macular Integrity Assessment (MAIA) device
- National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI VFQ-25)
- Functional Reading Independence Index (FRI) composite score

*Patients must meet following criteria: (a) able to detect fixation target, (b) total elapsed time to complete 68-point exam <30 min, (c) reliability test ratio <20%, (d) willing and able to undertake microperimetry in investigator's opinion.

BCVA=best-corrected visual acuity; FAF=fundus autofluorescence; LL-BCVA=low-luminance BCVA; GA=geographic atrophy.

Key demographics and baseline study eye characteristics

Characteristic		OAKS PM (N=202)	OAKS PEOM (N=205)	OAKS Sham Pooled (N=206)
Age, mean (SD)		78.8 (7.24)	78.1 (7.74)	78.6 (7.26)
Female, n (%)		125 (61.9%)	117 (57.1%)	133 (64.6%)
Male, n (%)		77 (38.1%)	88 (42.9%)	73 (35.4%)
Geographic region				
US, n (%)		147 (72.8%)	142 (69.3%)	147 (71.4%)
ROW, n (%)		55 (27.2%)	63 (30.7%)	59 (28.6%)
Caucasian, n (%)		185 (91.6%)	189 (92.2%)	187 (90.8%)
GA lesion size (mm^2), mean (SD)		8.18 (3.893)	8.29 (3.904)	8.20 (3.722)
Square root GA lesion size (mm), mean (SD)		2.78 (0.682)	2.80 (0.674)	2.79 (0.649)
GA lesion size, n (%)	<7.5 mm^2	101 (50.0%)	99 (48.3%)	104 (50.5%)
GA lesion location, n (%)	Extrafoveal	**86 (42.6%)**	74 (36.1%)	60 (29.1%)
GA lesion focality, n (%)	Unifocal	59 (29.2%)	62 (30.2%)	68 (33.0%)
Intermediate/large drusen, n (%)	>20	93 (46.0%)	104 (50.7%)	103 (50.0%)
NL-BCVA (ETDRS letters), mean (SD)		61.0 (15.30)	58.2 (17.03)	57.5 (16.57)

These analyses were performed on the modified intention-to-treat (mITT) population. The mITT population was 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; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PM=pegcetacoplan monthly; PEOM=pegcetacoplan every other month; ROW=rest of world; SD=standard deviation; US=United States.

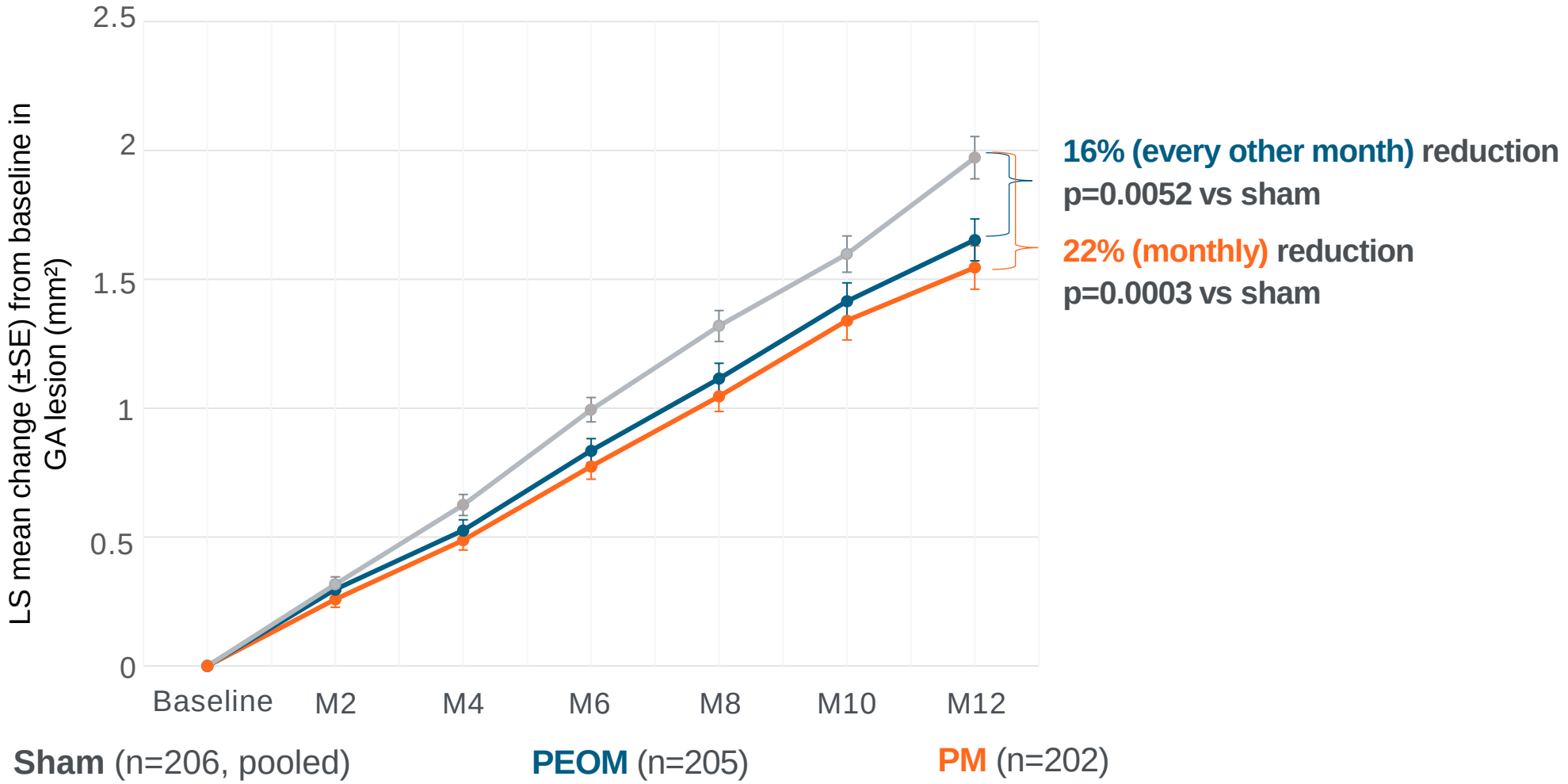
Key demographics and baseline study eye characteristics

		DERBY		
Characteristic		PM (N=201)	PEOM (N=200)	Sham Pooled (N=194)
Age, mean (SD)		78.7 (6.91)	79.2 (7.07)	78.6 (7.29)
Female, n (%)		118 (58.7%)	120 (60.0%)	122 (62.9%)
Male, n (%)		83 (41.3%)	80 (40.0%)	72 (37.1%)
Geographic region				
US, n (%)		142 (70.6%)	122 (61.0%)	122 (62.9%)
ROW, n (%)		59 (29.4%)	78 (39.0%)	72 (37.1%)
Caucasian, n (%)		187 (93.0%)	185 (92.5%)	187 (96.4%)
GA lesion size (mm^2), mean (SD)		8.36 (4.182)	8.22 (3.886)	8.26 (4.260)
Square root GA lesion size (mm), mean (SD)		2.80 (0.723)	2.79 (0.677)	2.78 (0.734)
GA lesion size, n (%)	<7.5 mm^2	99 (49.3%)	98 (49.0%)	94 (48.5%)
GA lesion location, n (%)	Extrafoveal	72 (35.8%)	81 (40.5%)	73 (37.6%)
GA lesion focality, n (%)	Unifocal	54 (26.9%)	53 (26.5%)	**66 (34.0%)**
Intermediate/large drusen, n (%)	>20	78 (38.8%)	78 (39.0%)	**98 (50.5%)**
NL-BCVA (ETDRS letters), mean (SD)		59.5 (17.40)	58.9 (15.97)	59.1 (16.85)

These analyses were performed on the modified intention-to-treat (mITT) population. The mITT population was 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.

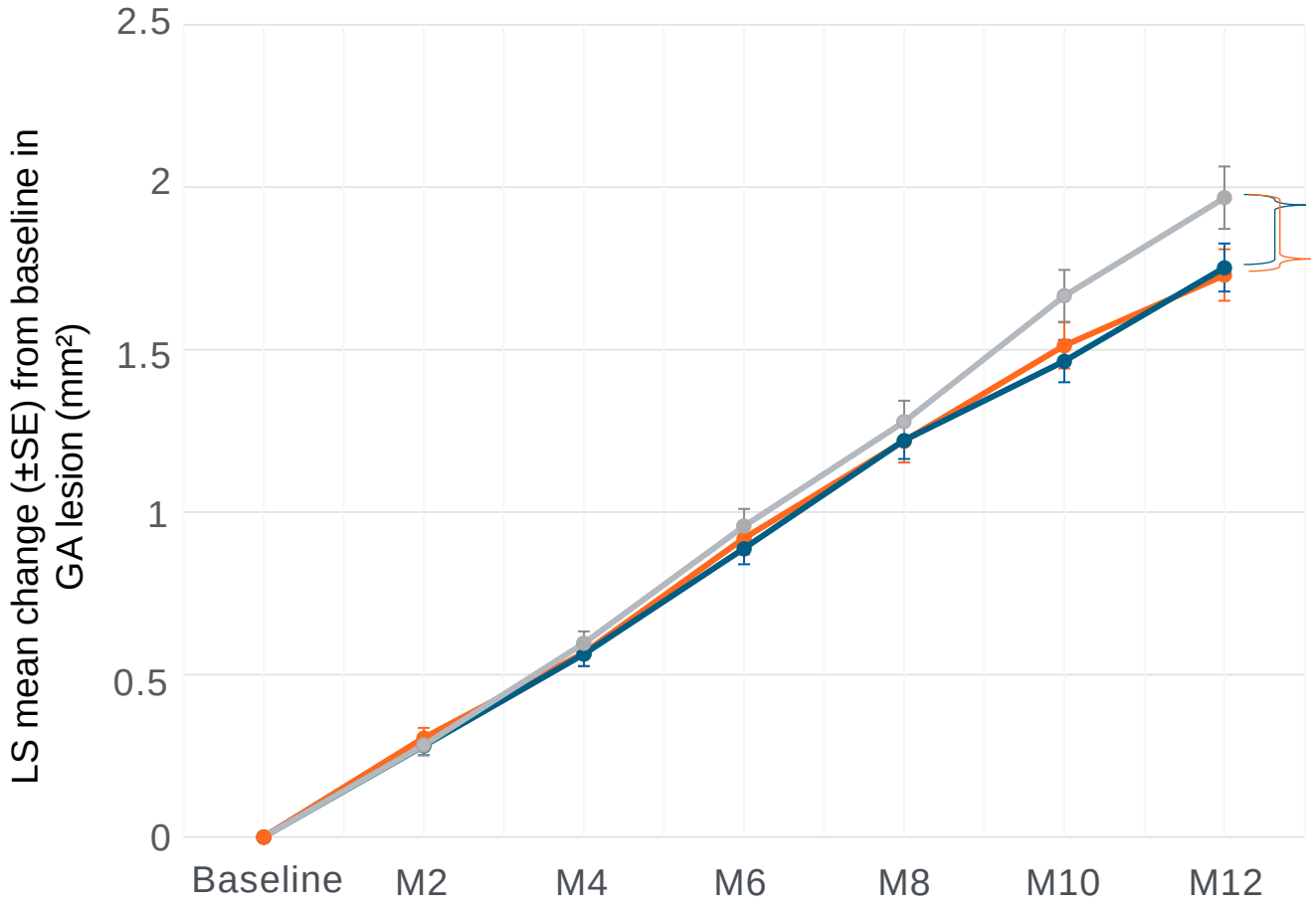
GA=geographic atrophy; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PM=pegcetacoplan monthly; PEOM=pegcetacoplan every other month; ROW=rest of world; SD=standard deviation; US=United States.

Pegcetacoplan monthly and every other month met the primary endpoint in **OAKS**



LS means estimated from a mixed-effects model for repeated measures (MMRM). 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.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan did not meet the primary endpoint in **DERBY**



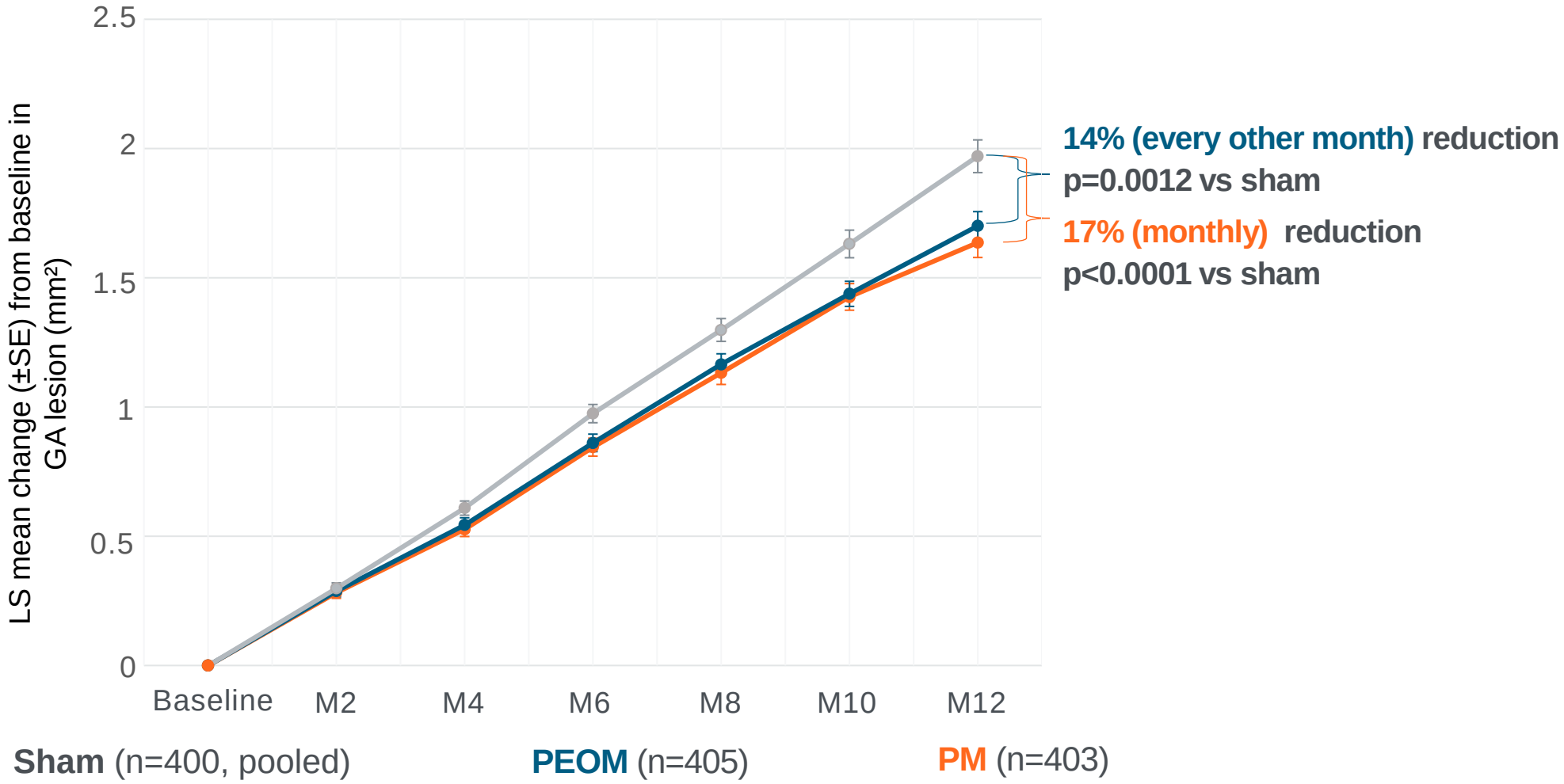
11% (every other month) reduction
p=0.0750 vs sham

12% (monthly) reduction
p=0.0528 vs sham

Sham (n=194, pooled) **PEOM** (n=200) **PM** (n=201)

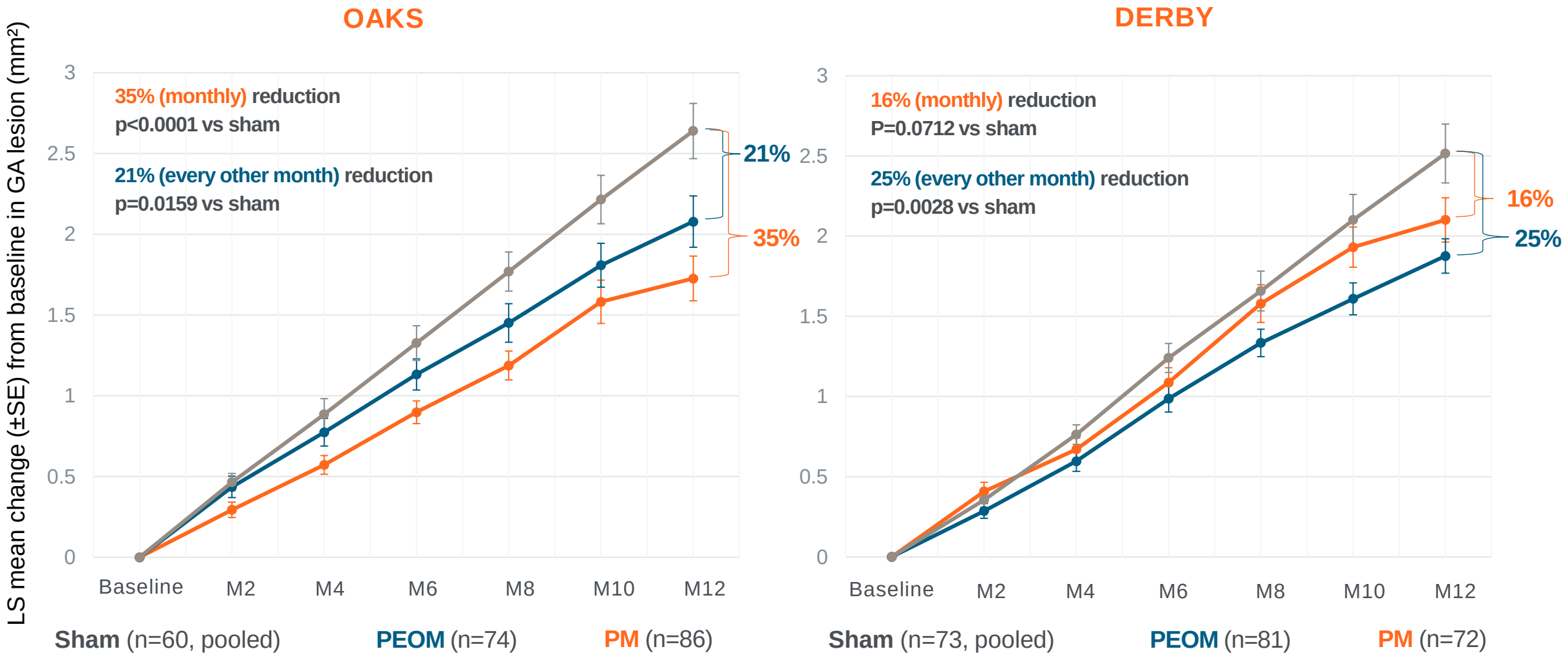
LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in a prespecified analysis of **OAKS and DERBY** combined



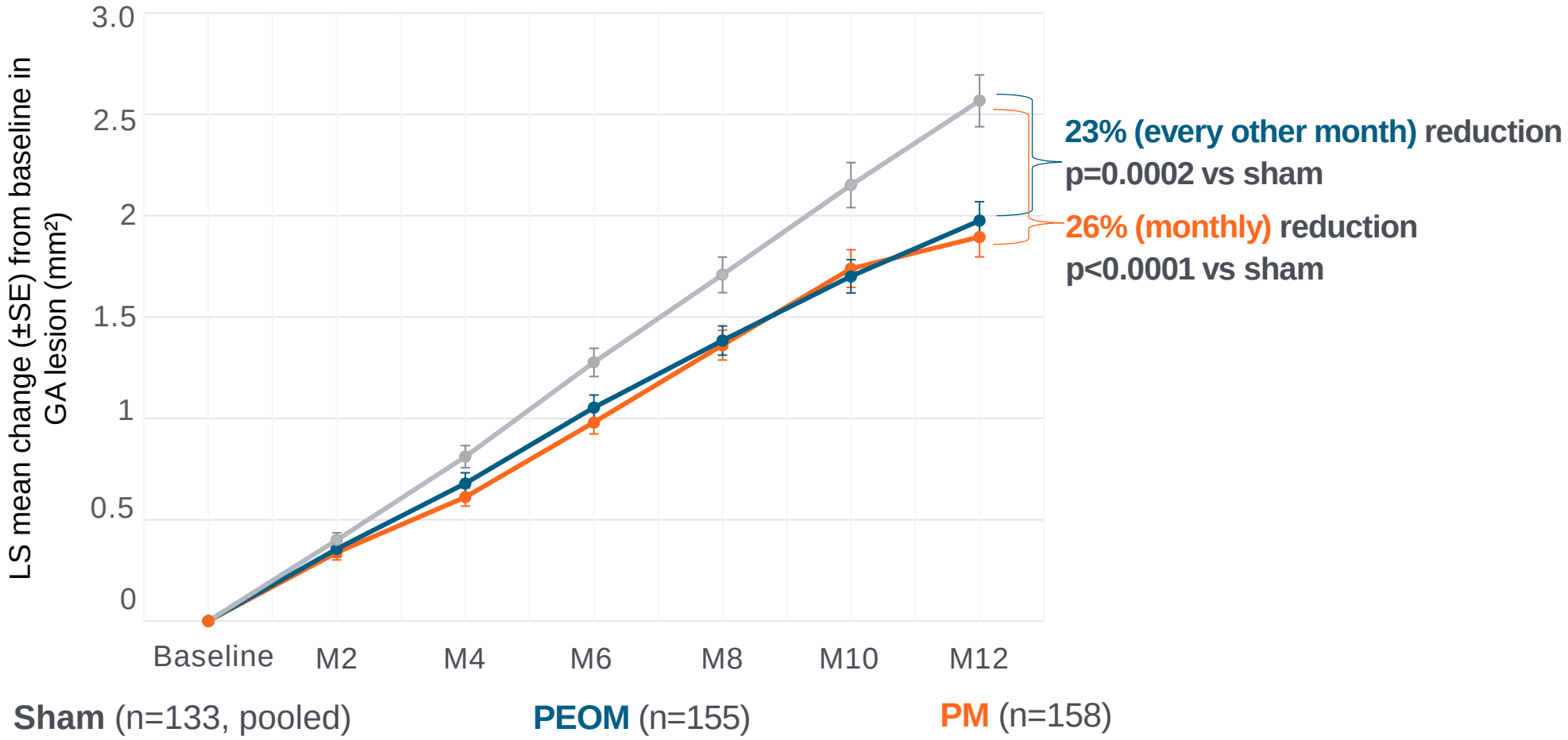
LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in patients with **extrafoveal** lesions in a prespecified analysis



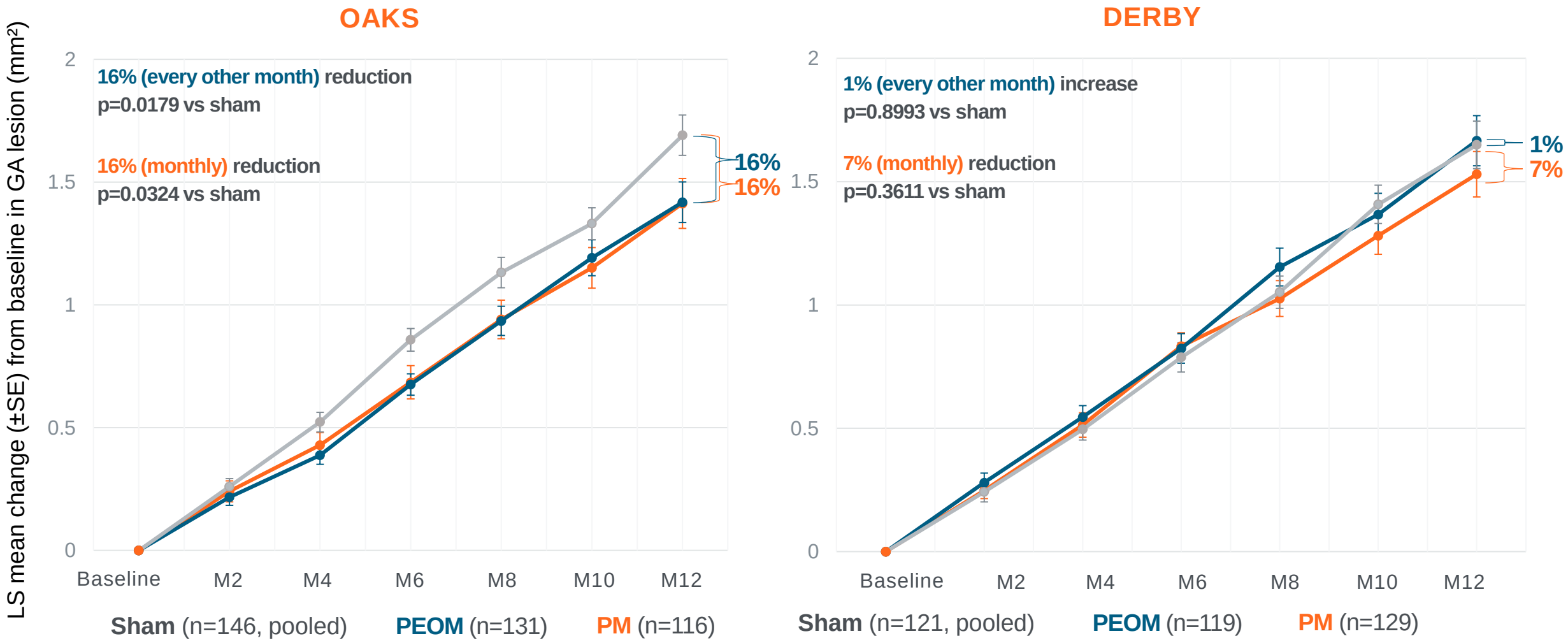
LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in patients with **extrafoveal** lesions in a prespecified combined analysis



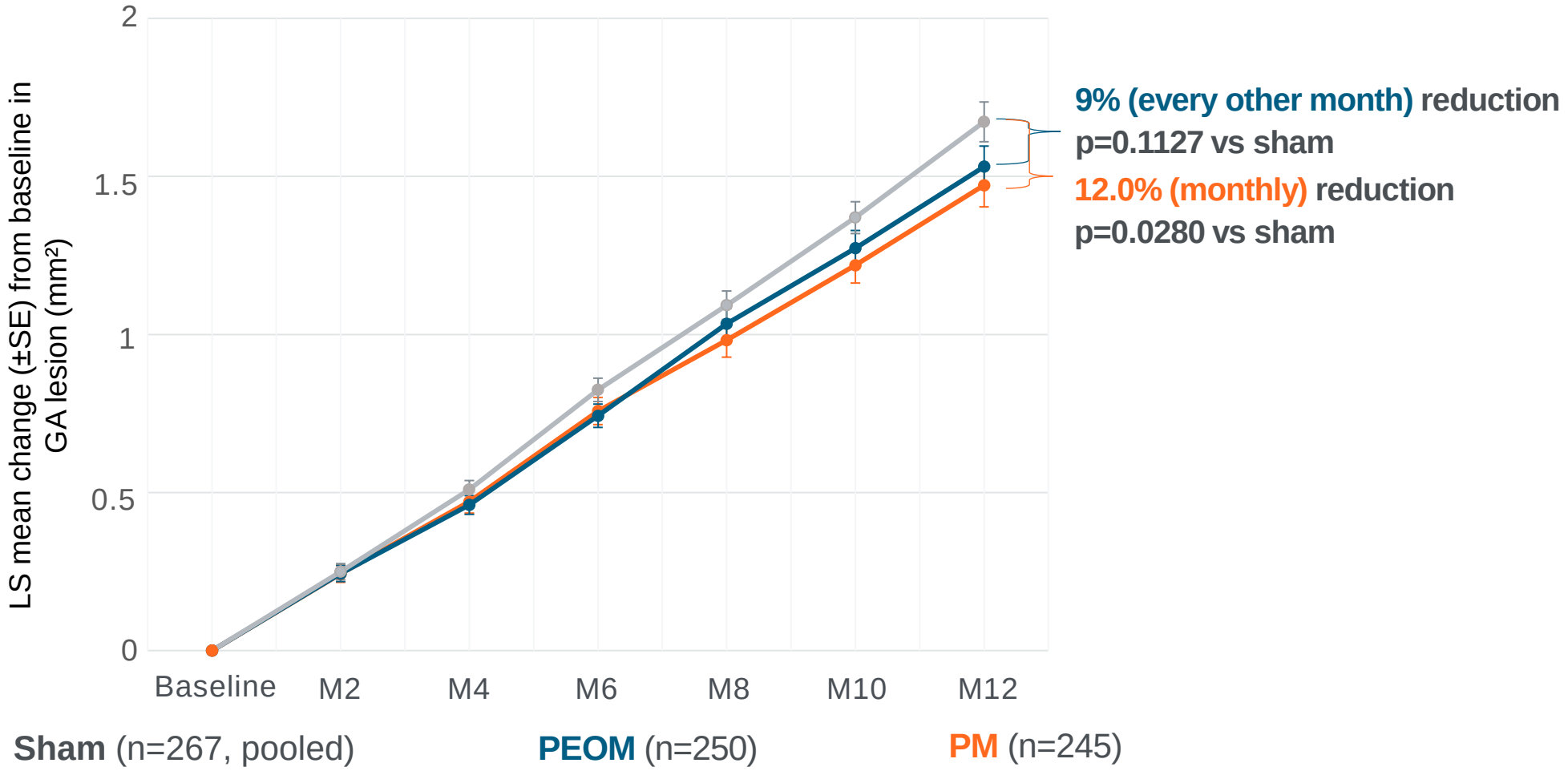
LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in patients with **foveal** lesions in **OAKS** in a prespecified analysis



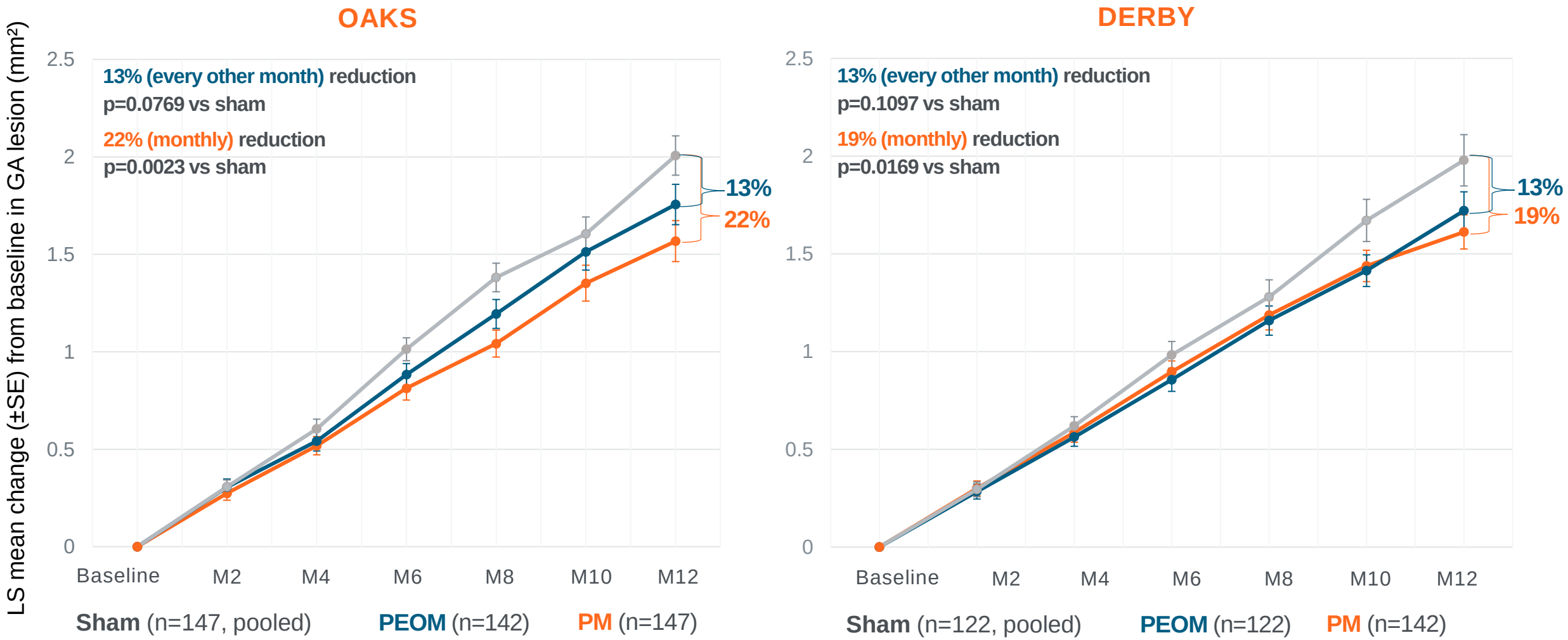
LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Pegcetacoplan reduced lesion growth in patients with **foveal** lesions in a prespecified combined analysis



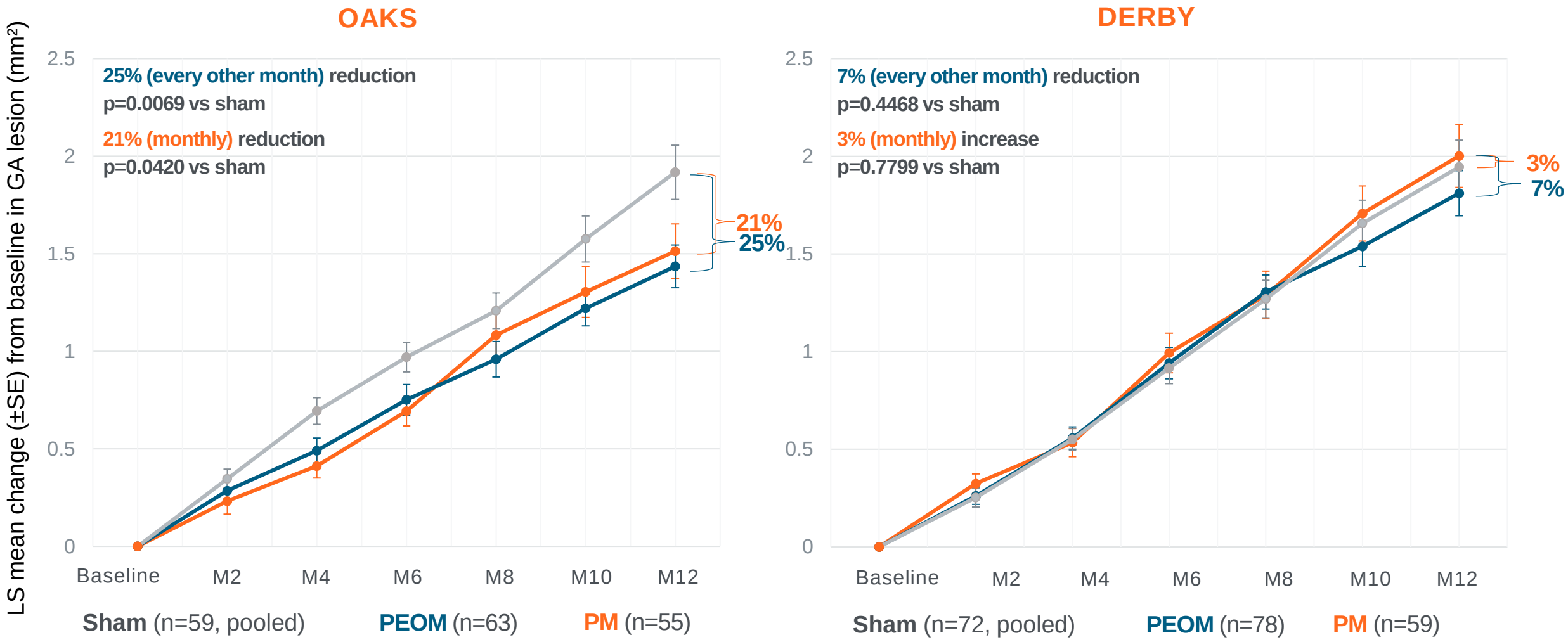
LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Prespecified subgroup analysis: United States sites



LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Prespecified subgroup analysis: Rest of World sites



LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis.
GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Analysis of fellow eye vs study eye lesion growth

- Patients with bilateral GA were included in this analysis
- In addition, for a subject to be included, the fellow eye had to meet the following criteria:
  - Absence of CNV in the medical history
  - Baseline GA lesion size between 2.5 and 17.5 mm^2
  - Presence of any pattern of hyperautofluorescence in the junctional zone of GA
  - GA not confluent with peripapillary atrophy

CNV=choroidal neovascularization; GA=geographic atrophy.

Pegcetacoplan reduced lesion growth in an analysis of the study eye vs untreated fellow eye, supporting primary analysis

OAKS AND DERBY

Sham pooled (n=195)

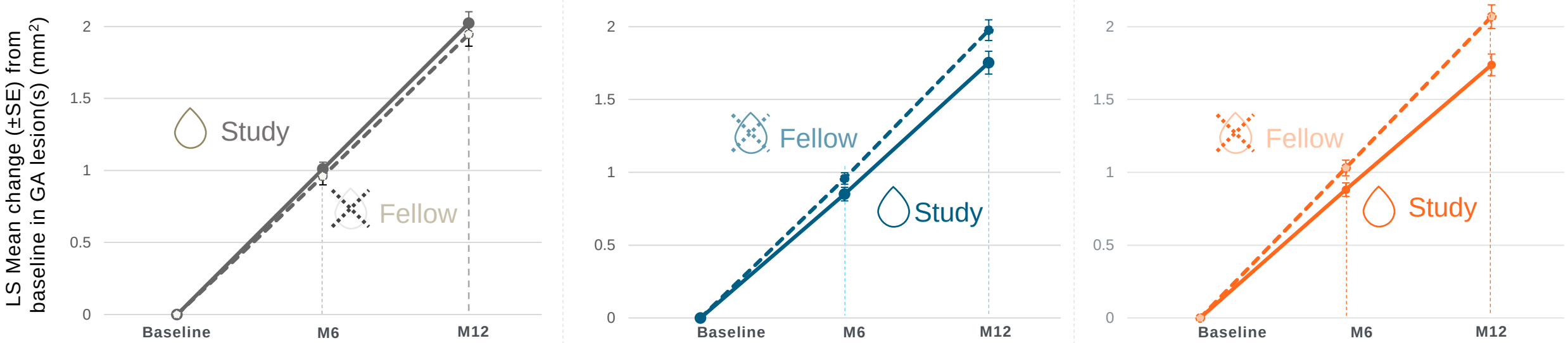
4% faster growth vs fellow eye
p = 0.2666

PEOM (n=211)

11% slower growth vs fellow eye
p = 0.0011

PM (n=177)

16% slower growth vs fellow eye
p < 0.0001



In DERBY and OAKS, study eye vs fellow eye comparison was prespecified; statistical modeling was performed post-hoc. LS means estimated from a mixed-effects model for repeated measures. The modified intention-to-treat population was used for the analysis. In addition, patients must have bilateral GA and a fellow eye that meets the following key characteristics at baseline: absence of CNV in the medical history; baseline GA lesion size between 2.5 and 17.5 mm^2 and have at least one study eye or fellow eye at measurement at Month 6 or Month 12. In the FILLY analysis, all bilateral GA patients are included. CNV=choroidal neovascularization; GA=geographic atrophy; LS=least square; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Post-hoc covariate analysis: Background

- Question: What is the real effect size of pegcetacoplan?

- Apellis has taken a multi-pronged approach to understand inconsistent results across trials, including a significant investigation of study operations, regional differences, as well as imbalances in baseline characteristics that impact lesion growth

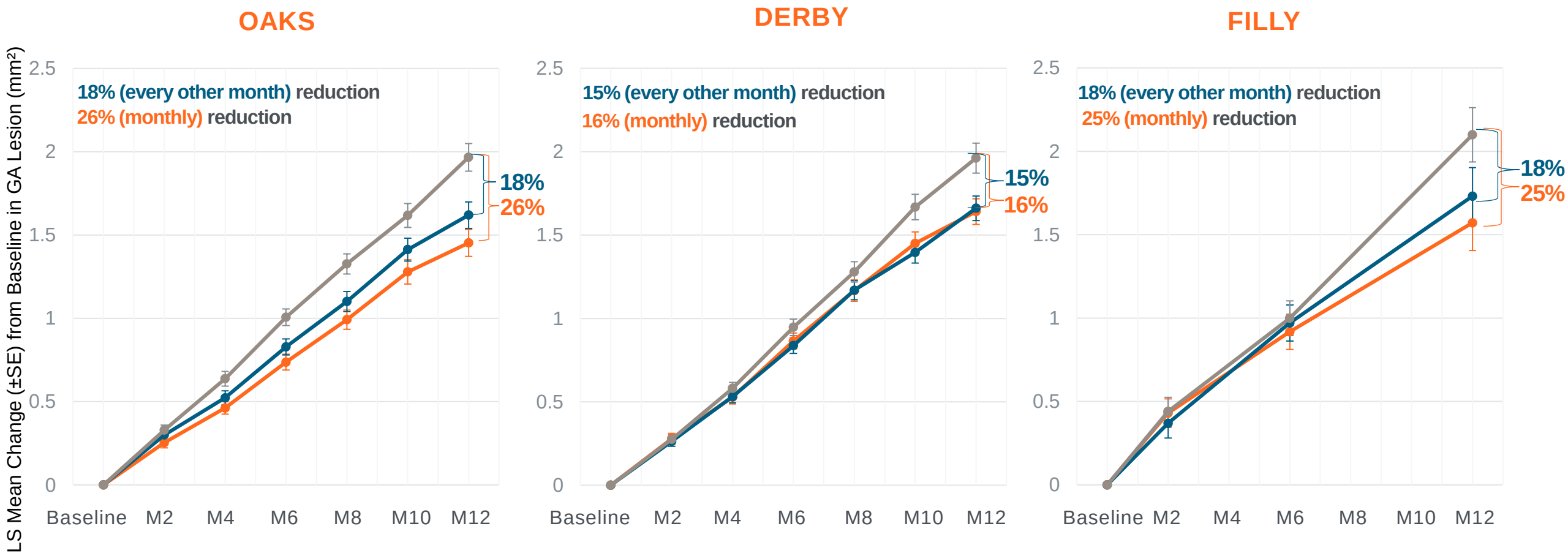
- We undertook a post-hoc analysis to examine the potential contribution of baseline characteristic imbalances on the diverging results. The 8 most relevant variables related to GA were investigated for imbalance, and analyses were re-run adjusting for the imbalanced variables:

Study eye focality • Imbalanced in DERBY (*favoring sham*) **Study eye lesion location** • Imbalanced in OAKS (*favoring sham*) **Study eye lesion size** **Study eye pseudodrusen**	**Study eye low luminance deficit** • Imbalanced in FILLY (*favoring PM*) **Region** **GA laterality** **Study eye intermediate/large drusen** • Imbalanced in DERBY (*favoring sham*) and FILLY (favo*ring PEOM*)

- We are presenting initial findings from this investigation

GA=geographic atrophy; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly.

Converging treatment effect of pegcetacoplan across OAKS, DERBY, in FILLY in covariate-adjusted post-hoc analysis



OAKS			DERBY			FILLY		
Sham (n=205, pooled)	**PEOM** (n=205)	**PM** (n=202)	**Sham** (n=194, pooled)	**PEOM** (n=200)	**PM** (n=201)	**Sham** (n=80, pooled)	**PEOM** (n=78)	**PM** (n=84)

LS means estimated from a mixed-effects model for repeated measures. The mITT population was used for the analysis.
SE=standard error; PM, pegcetacoplan monthly; PEOM, pegcetacoplan every other month.

Conclusions

- Pegcetacoplan monthly and every other month met the primary endpoint in OAKS
- Pegcetacoplan monthly and every other month did not meet the primary endpoint in DERBY
- Pegcetacoplan demonstrated greater efficacy in patients with extrafoveal lesions at baseline
- OAKS, DERBY, and FILLY all show consistent efficacy of pegcetacoplan in treated study eyes versus untreated fellow eyes
- In a post-hoc analysis, after correcting for disparities in baseline characteristics, OAKS, DERBY, and FILLY results are more convergent. Investigation is still ongoing
- The pegcetacoplan GA development program includes over 1,500 patients across OAKS, DERBY, and FILLY, collectively demonstrating slowing of GA progression by pegcetacoplan monthly and every other month

GA=geographic atrophy.