Financial Disclosure

- I have the following financial interests or relationships to disclose:
  - Alcon Laboratories, Inc.: Consultant/Advisor
  - American Society of Retina Specialists: Executive Role
  - Apellis Pharmaceuticals, Inc.: Consultant/Advisor, Grant Support
  - AsclepiX Therapeutics: Consultant/Advisor
  - Bausch + Lomb: Consultant/Advisor
  - GENENTECH: Consultant/Advisor, Grant Support
  - Gyroscope: Consultant/Advisor
  - Novartis: Consultant/Adviso, Grant Support
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Efficacy of Intravitreal Pegcetacoplan in Geographic Atrophy: 24-Month Results from the Phase 3 OAKS and DERBY Trials

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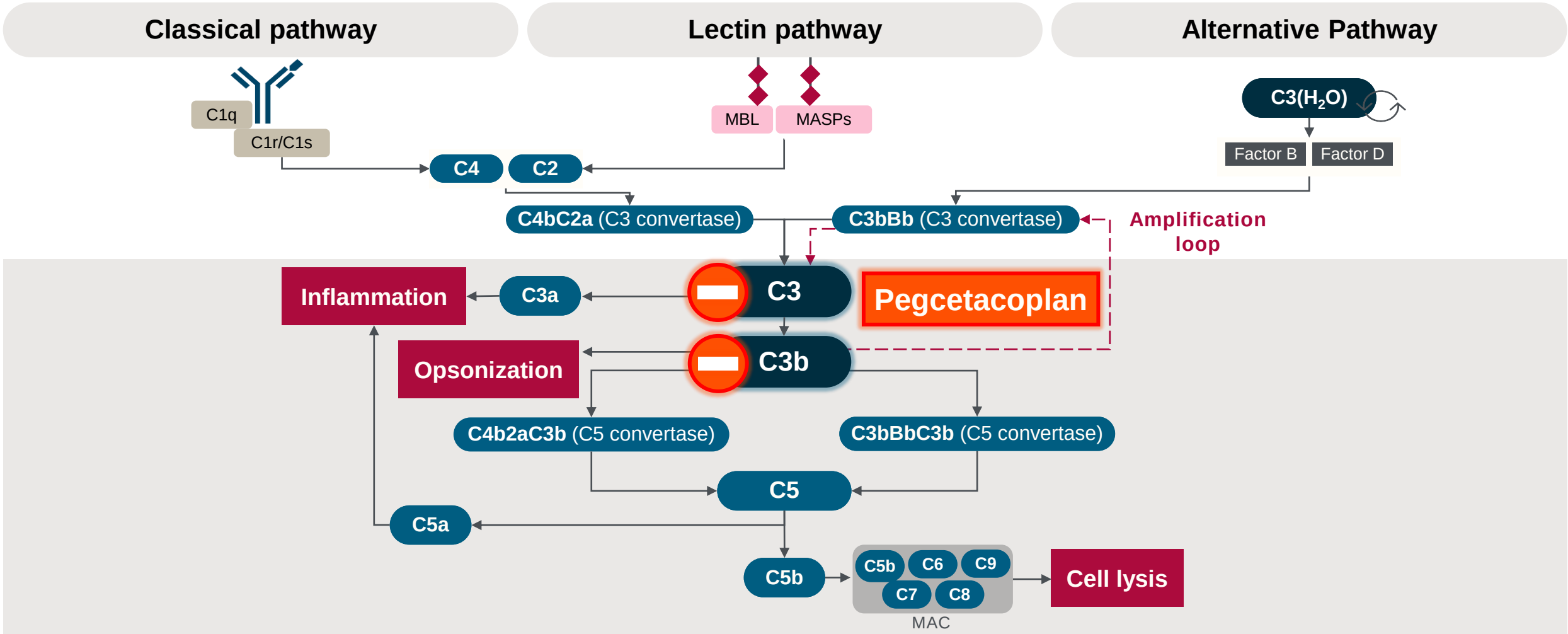
Pegcetacoplan binds to C3 and C3b, inhibiting the downstream effects of the complement pathway[1–6]



MAC=membrane attack complex; MBL=mannose-binding lectin; MASP=MBL-associated serine protease.

1. Kolev M et al. *Nat Rev Immunol* 2014;14:811–20; 2. Holers VM. *Annu Rev Immunol* 2014;32:433–59; 3. Dunkelberger JR, Song WC. *Cell Res* 2010;20:34–50; 4. Strunz T et al. *Sci Rep* 2020;10:1584; 5. Anderson DH et al. *Am J Ophthalmol* 2002;134:411–31; 6. Boyer DS et al. *Retina* 2017;37:819–35.

Design of the Phase 3 OAKS and DERBY studies

OAKS DERBY

Patients with GA secondary to AMD
~1200 patients at ~200 sites in the combined studies (1258 randomized in total)

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

Prespecified secondary endpoints at 24 months

- BCVA[a], LL-BCVA
- Reading speed[a]
- NEI VFQ-25
- FRI Index score[a]
- Microperimetry (OAKS only)[a] – MAIA device
- Lesion growth

GALE 3-year open-label extension study

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*

OAKS, DERBY, GALE CT.gov identifiers: NCT03525613, NCT03525600, NCT04770545, respectively. [a]Key secondary endpoints. AMD=age-related macular degeneration; BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; EOM=every other month; FRI=Functional Reading Independence; GA=geographic atrophy; LL=low luminance; MAIA=macular integrity assessment; MMRM=mixed-effects model for repeated measures; NEI-VFQ=National Eye Institute Visual Function Questionnaire.

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
  - GA lesions with or without subfoveal involvement 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, or active, CNV in the fellow eye is not exclusionary

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

Key demographics and baseline study eye characteristics

Characteristic	OAKS		
	PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)
Age, mean (SD)	78.8 (7.24)	78.1 (7.74)	78.6 (7.25)
Female, n (%)	125 (61.9%)	117 (57.1%)	133 (64.3%)
Male, n (%)	77 (38.1%)	88 (42.9%)	74 (35.7%)
Geographic region			
US, n (%)	147 (72.8%)	142 (69.3%)	148 (71.5%)
ROW, n (%)	55 (27.2%)	63 (30.7%)	59 (28.5%)
Caucasian, n (%)	185 (91.6%)	189 (92.2%)	188 (90.8%)
GA lesion size (mm^2), mean (SD)	8.18 (3.895)	8.30 (3.904)	8.21 (3.712)
Square root GA lesion size (mm), mean (SD)	2.78 (0.682)	2.80 (0.674)	2.79 (0.647)
GA lesion size <7.5 mm^2, n (%)	101 (50.0%)	98 (47.8%)	104 (50.2%)
Nonsubfoveal / extrafoveal lesion (location), n (%)	**86 (42.6%)**	**74 (36.1%)**	**60 (29.0%)**
Unifocal lesion (focality), n (%)	59 (29.2%)	62 (30.2%)	68 (32.9%)
Intermediate/large drusen >20, n (%)	93 (46.0%)	104 (50.7%)	104 (50.2%)
NL-BCVA (ETDRS letters), mean (SD)	61.0 (15.30)	58.2 (17.03)	57.6 (16.59)

These analyses were performed on the 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. ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; mITT=modified intent-to-treat; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; ROW=rest of world; SD=standard deviation; US=United States.

Key demographics and baseline study eye characteristics

DERBY

Characteristic	PM (N=201)	PEOM (N=201)	Sham Pooled (N=195)
Age, mean (SD)	78.7 (6.91)	79.2 (7.08)	78.6 (7.28)
Female, n (%)	118 (58.7%)	120 (59.7%)	123 (63.1%)
Male, n (%)	83 (41.3%)	81 (40.3%)	72 (36.9%)
Geographic region			
US, n (%)	142 (70.6%)	122 (60.7%)	122 (62.6%)
ROW, n (%)	59 (29.4%)	79 (39.3%)	73 (37.4%)
Caucasian, n (%)	187 (93.0%)	186 (92.5%)	188 (96.4%)
GA lesion size (mm^2), mean (SD)	8.37 (4.181)	8.25 (3.894)	8.24 (4.261)
Square root GA lesion size (mm), mean (SD)	2.80 (0.722)	2.79 (0.678)	2.78 (0.734)
GA lesion size <7.5 mm^2, n (%)	99 (49.3%)	98 (48.8%)	95 (48.7%)
Nonsubfoveal / extrafoveal lesion (location), n (%)	**72 (35.8%)**	**81 (40.3%)**	**73 (37.4%)**
Unifocal lesion (focality), n (%)	54 (26.9%)	53 (26.4%)	66 (33.8%)
Intermediate/large drusen >20, n (%)	78 (38.8%)	78 (38.8%)	98 (50.3%)
NL-BCVA (ETDRS letters), mean (SD)	59.5 (17.40)	58.7 (16.12)	59.0 (16.85)

These analyses were performed on the 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. ETDRS=Early Treatment Diabetic Retinopathy Study; GA=geographic atrophy; mITT=modified intent-to-treat; mm=millimeters; n=number of patients; NL-BCVA=normal luminance best-corrected visual acuity; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; ROW=rest of world; SD=standard deviation; US=United States.

Patient disposition and exposure at Month 24

	OAKS			DERBY		
ITT set	PM (N=213)	PEOM (N=212)	Sham Pooled (N=212)	PM (N=206)	PEOM (N=208)	Sham Pooled (N=207)
Completed study through Month 24, n (%)	144 (67.6%)	169 (79.7%)	158 (74.5%)	147 (71.4%)	161 (77.4%)	161 (77.8%)
Discontinued study prior to Month 24, n (%)	69 (32.4%)	43 (20.3%)	54 (25.5%)	59 (28.6%)	47 (22.6%)	46 (22.2%)

19% (60/318) of study discontinuations were attributed to COVID-19

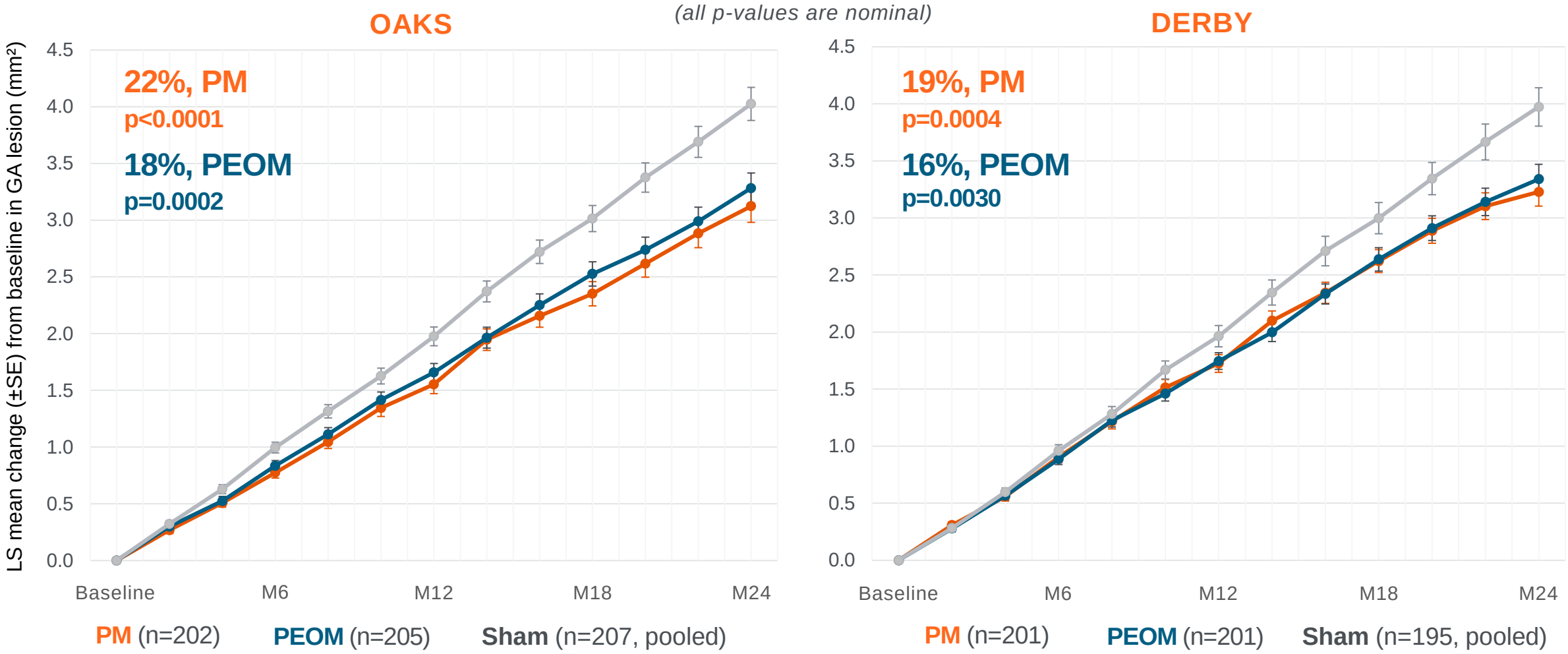
mITT set	PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)	PM (N=201)	PEOM (N=201)	Sham Pooled (N=195)
Mean number of injections/patient, n (SD)	18.9 (6.08)	10.2 (2.92)	14.4 (6.50)	18.7 (6.09)	10.0 (2.80)	14.7 (6.46)
Mean compliance, %	87.4%	90.5%	87.9%	85.6%	89.0%	88.7%

Compliance % = injections administered/injections scheduled up to study completion or treatment discontinuation x 100

The ITT set includes all randomized patients. mITT = modified ITT, 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 geographic atrophy lesion area in the study eye. ITT=intent-to-treat; N=number of patients; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SD=standard deviation.

Reductions in GA lesion growth at Month 24

(all p-values are nominal)

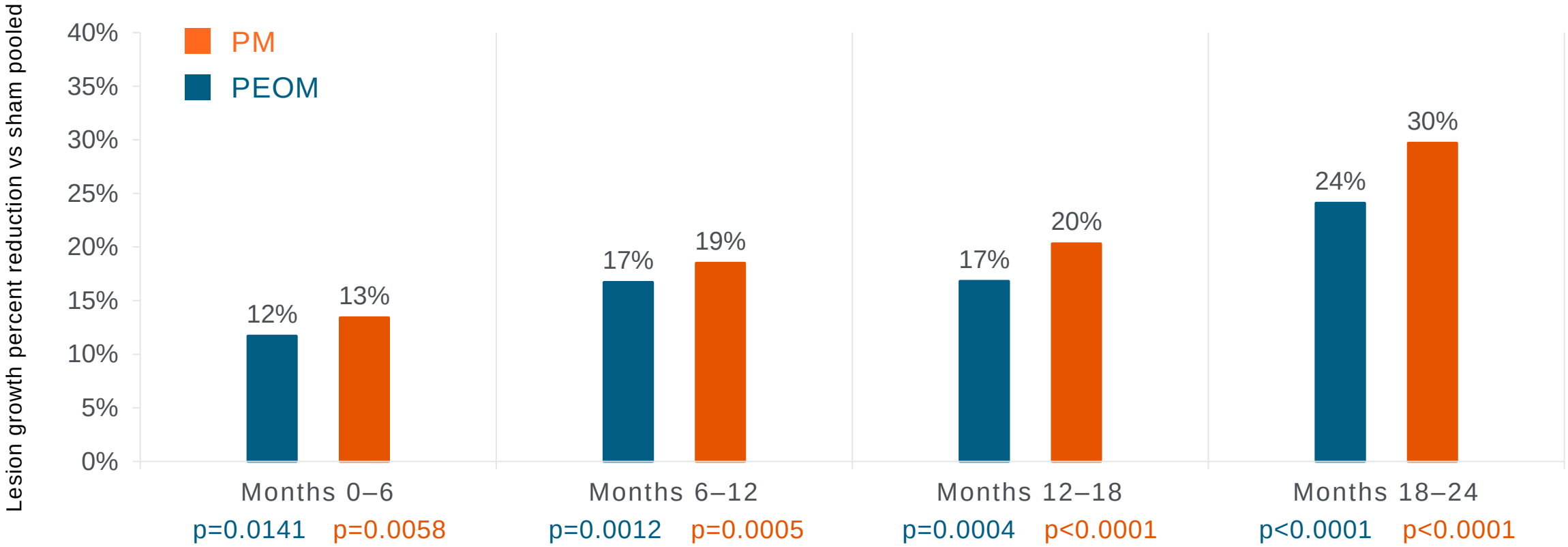


LS means estimated from MMRM analysis. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.
GA=geographic atrophy; LS=least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

OAKS and DERBY combined

Reductions in GA lesion growth by 6-month periods

Post hoc piecewise linear analysis; all data represented are from OAKS and DERBY combined (all p-values are nominal)

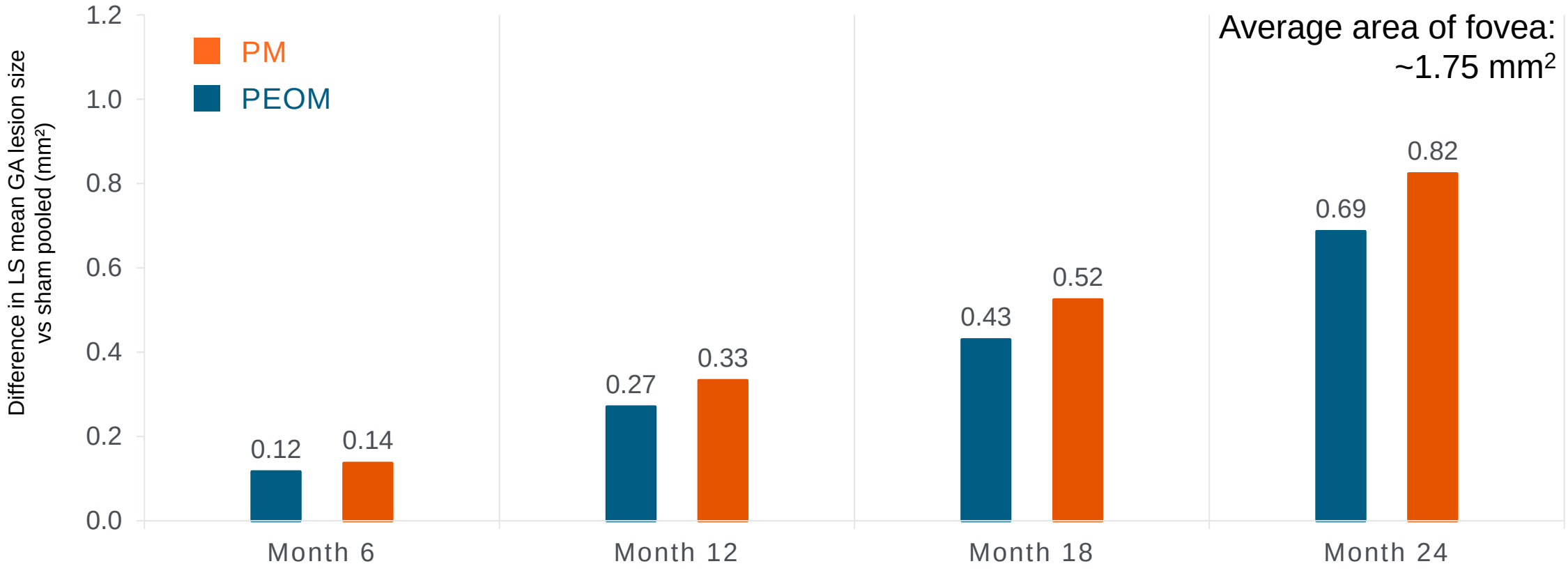


Percent reduction vs sham pooled for Month 0 to Month 24 was estimated from a piecewise linear slope model with 6-month segments using the combined patient-level data, not a simple average of results, from the two studies. Point estimates for the Month 0 to Month 18 segments vary marginally from previously reported numbers due to the inclusion of the Month 20 to Month 24 data into the statistical model.

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

OAKS and DERBY combined

Cumulative preservation of retinal tissue over 24 months

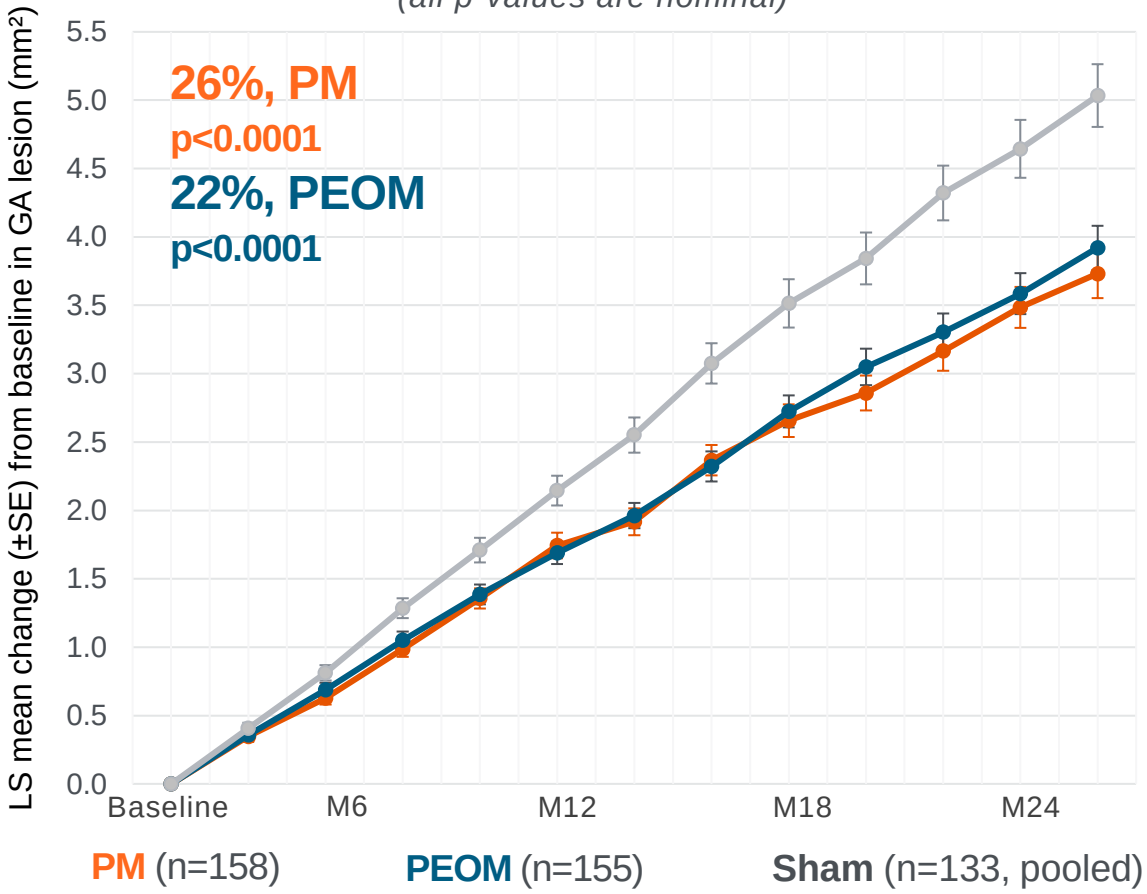


Absolute cumulative difference in lesion size vs pooled sham at Month 6, Month 12, Month 18, and Month 24 ('preserved area') from main MMRM analysis of mITT population. Fovea size calculated from average diameter of 1.5 mm per Kolb et al., *The Architecture of the Human Fovea.* GA=geographic atrophy;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

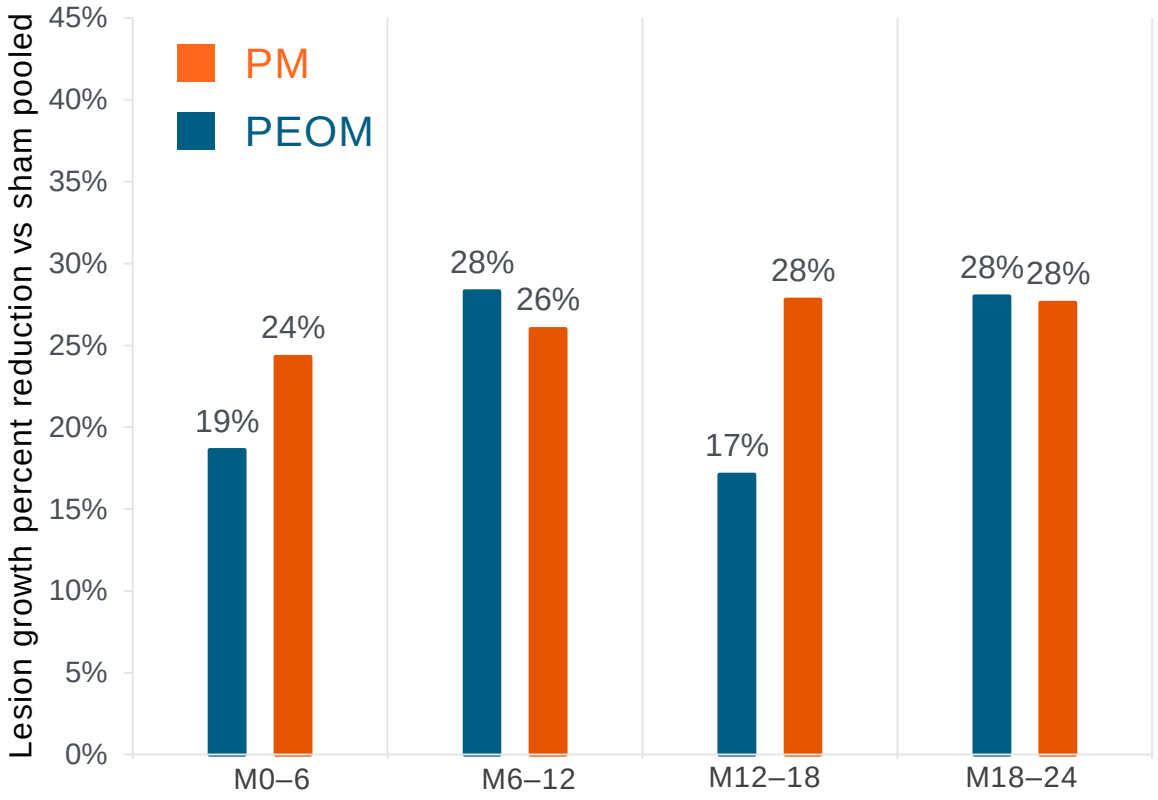
OAKS and DERBY combined

Nonsubfoveal subgroup: Reductions in GA lesion growth

Reductions in GA lesion growth by lesion location (all p-values are nominal)[a]



Post hoc piecewise linear analysis[b]

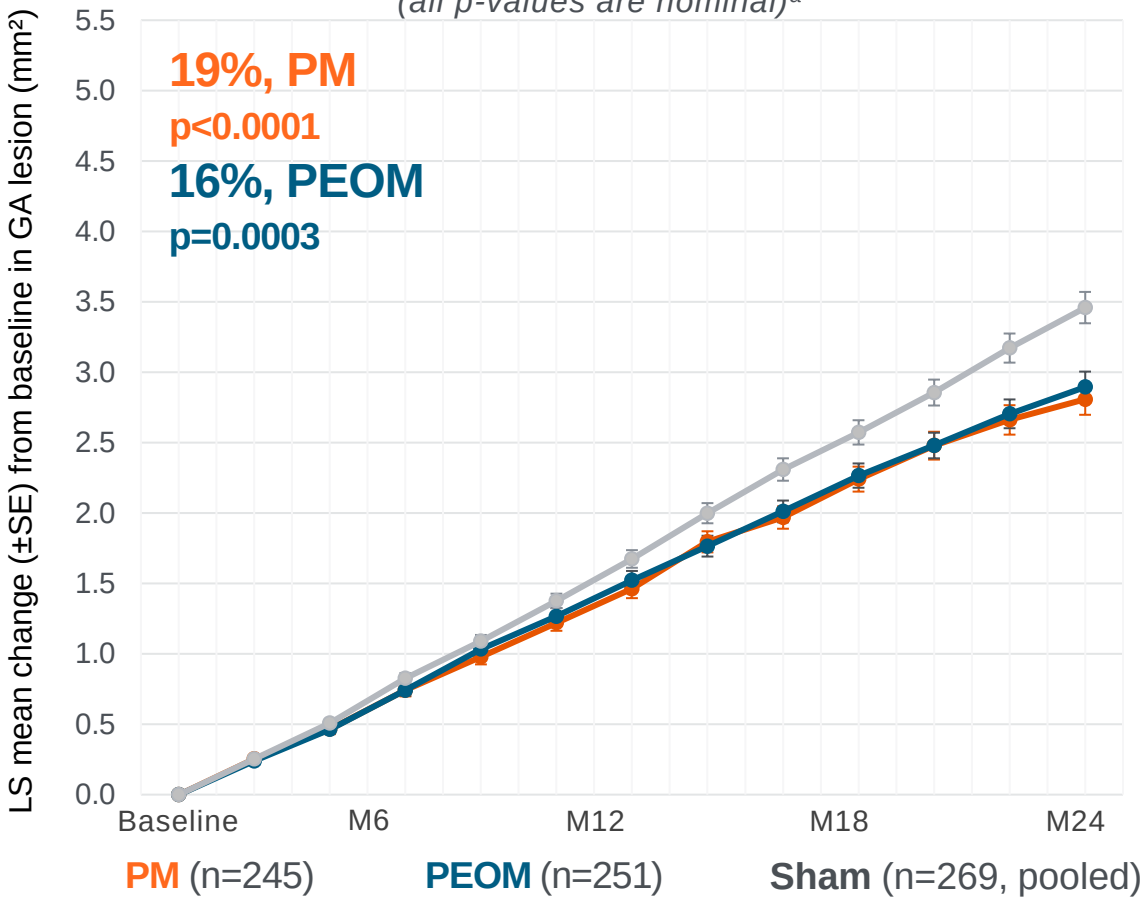


Nonsubfoveal synonymous with extrafoveal. [a]LS means estimated from MMRM analysis. The mITT population was used for the analysis. [b]Percent reduction vs pooled sham for Month 0 to Month 24 was estimated from a piecewise linear slope model with 6-month segments using the combined patient-level data, not a simple average of results, from the two studies. GA=geographic atrophy; LS=least square; M=month; mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

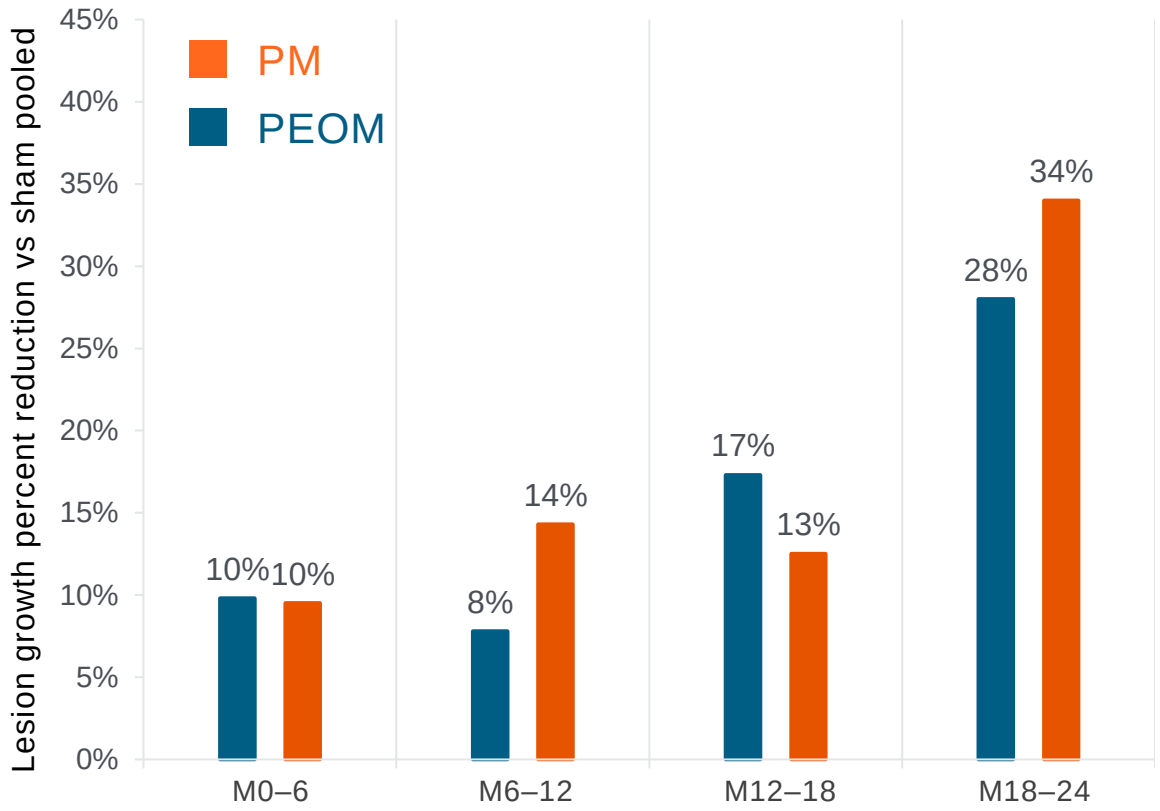
OAKS and DERBY combined

Subfoveal subgroup: Reductions in GA lesion growth

Reductions in GA lesion growth by lesion location (all p-values are nominal)[a]



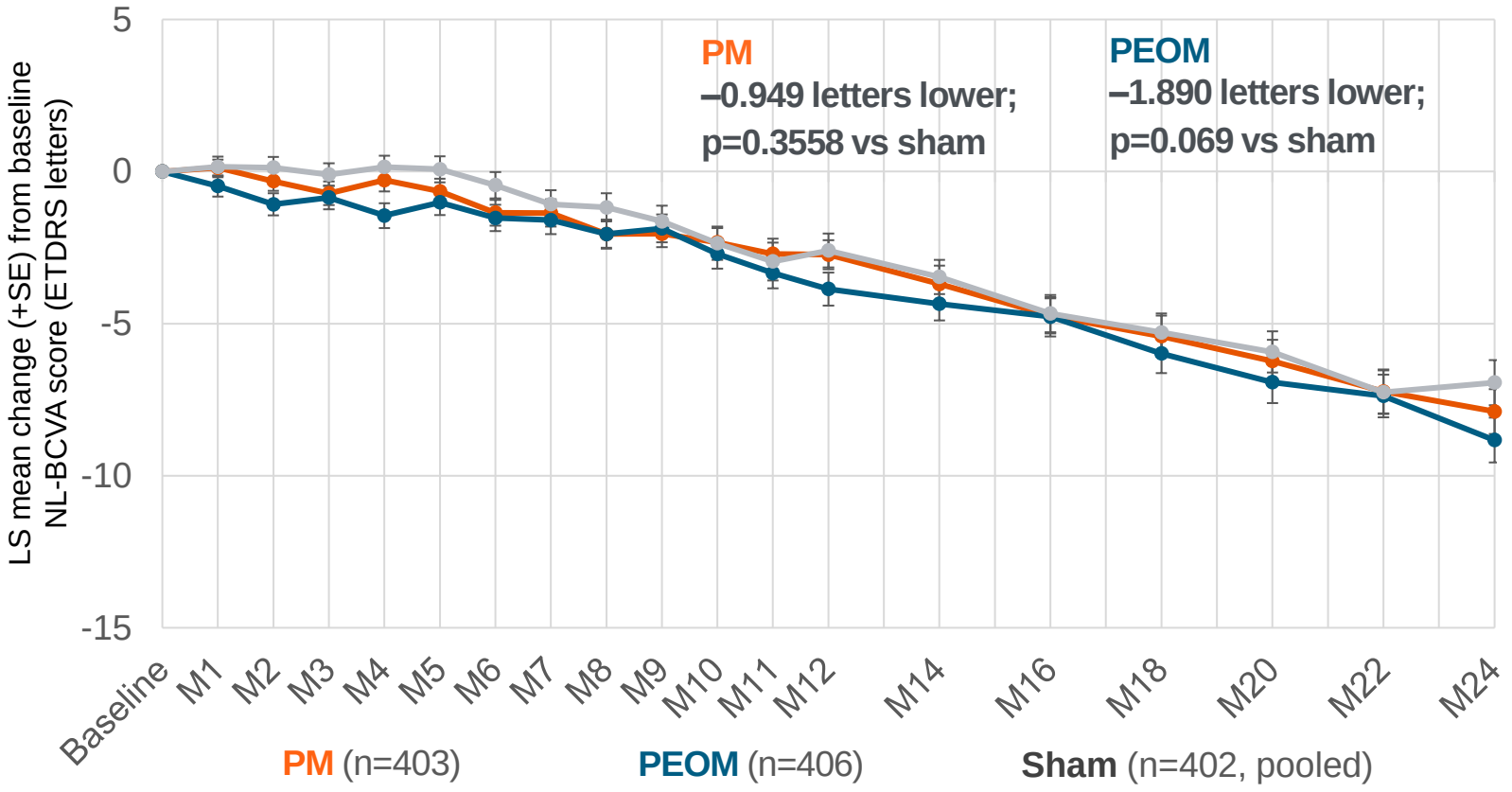
Post hoc piecewise linear analysis[b]



Subfoveal synonymous with foveal. [a]LS means estimated from MMRM analysis. The mITT population was used for the analysis. [b]Percent reduction vs pooled sham for Month 0 to Month 24 was estimated from a piecewise linear slope model with 6-month segments using the combined patient-level data, not a simple average of results, from the two studies. GA=geographic atrophy; LS=least square; M=month; mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

OAKS and DERBY combined

BCVA in the study eye over 24 months



Visual function endpoints:

No statistically significant differences across study arms on key secondary endpoints at 24 months

- BCVA
- Maximum reading speed
- Functional Reading Independence Index
- Microperimetry: Mean threshold sensitivity (OAKS only)

In nonsubfoveal subgroup, lesion distance to foveal center at baseline was larger in sham pooled (370 microns) than in PM (337 microns) and PEOM (340 microns)

LS means estimated from MMRM analysis. The mITT 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 one post-baseline value of GA lesion area in the study eye. BCVA=best-corrected visual acuity; ETDRS=Early Treatment of Diabetic Retinopathy Study; GA=geographic atrophy; LS=least square; M=month; mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures; NL=normal luminance; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Conclusions

Efficacy of pegcetacoplan in GA

- The pegcetacoplan development program includes >1200 patients over 24 months in two Phase 3 studies. The program enrolled a heterogeneous GA population with broad inclusion criteria, including patients with subfoveal and nonsubfoveal lesions

- Pegcetacoplan showed clinically meaningful reductions in GA lesion growth in the overall patient population at 24 months, with increased treatment effect seen between Months 18–24
  - Area of retina preserved (~0.7–0.8 mm^2) is meaningful in context of total area of fovea (~1.75 mm^2)

- Meaningful reductions in GA lesion growth were demonstrated in the nonsubfoveal subgroup (26% PM, 22% PEOM) as well as the subfoveal subgroup (19% PM and 16% PEOM) over 24 months

- The GALE extension study will provide longer-term data through up to 5 years of treatment for both monthly and EOM dosing

- Largest GA dataset across three registrational studies; FDA review is ongoing with PDUFA target action date of November 26, 2022, and EMA submission is planned by end of 2022

EMA=European Medicines Agency; EOM=every other month; FDA=Food and Drug Administration; GA=geographic atrophy; PDUFA=Prescription Drug User Fee Act; PEOM=pegcetacoplan EOM; PM=pegcetacoplan monthly.