Efficacy of intravitreal pegcetacoplan in geographic atrophy: 24-month results from the phase 3 OAKS and DERBY trials

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Disclosures

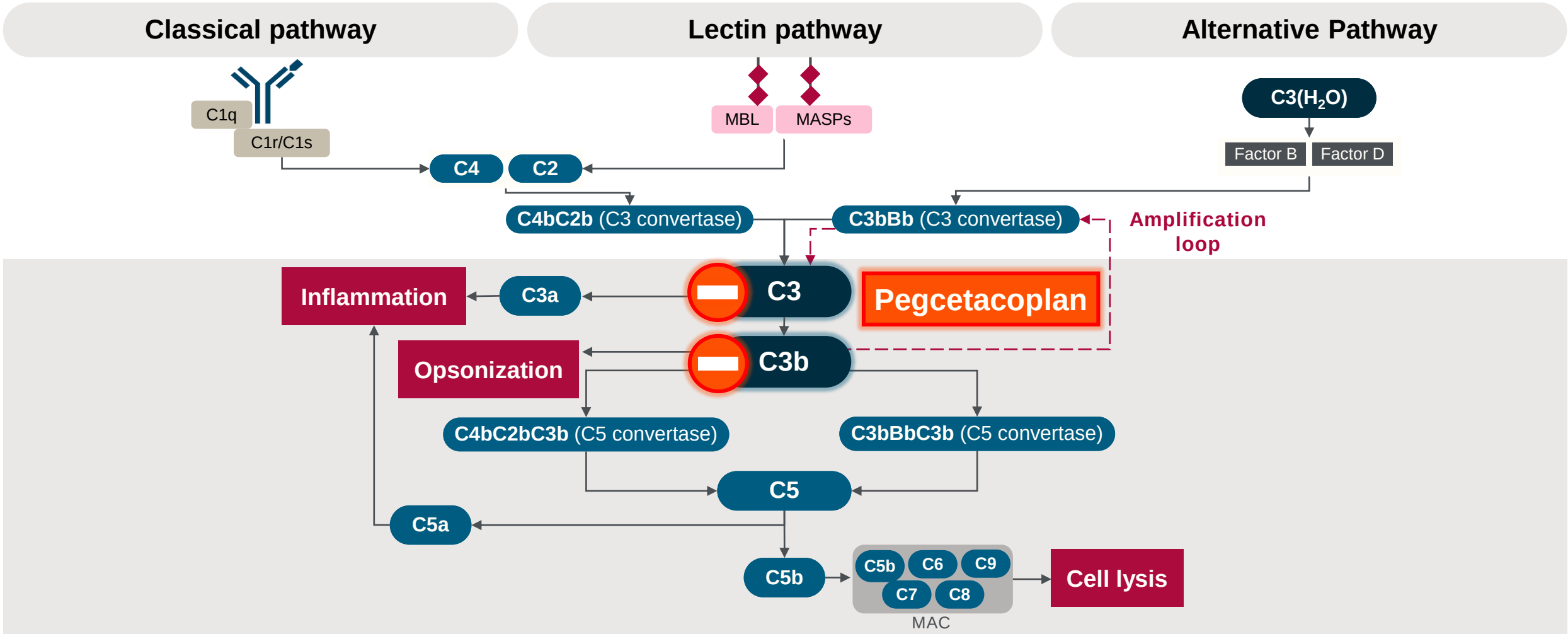
- I have the following financial interests or relationships to disclose:
  - Consultant: 4DMT, Abpro, Adverum, Aerie, Affamed, Allegro, Allergan, Allgenesis, Annexon, Apellis Pharmaceuticals, Aprea, Asclepix, Aviceda, BVT, Chengdu Kanghong Biotechnology, DTx, Eloxx, Galimedix, Graybug, Gyroscope, Horizon Therapeutics, IVERIC Bio, Laboratoires Thea, Lensgen, NGM Biopharmaceuticals, Novartis, Ocular Therapeutix, Oriole, Oxurion, Palatin, Regeneron, REGENXBIO, Roche/Genentech, Santen, Scifluor, Stealth Biotherapeutics, Surrozen, Verseon, and Vinci
  - Stockholder: Apellis Pharmaceuticals
  - Research grants: Apellis Pharmaceuticals
- Studies funded by Apellis Pharmaceuticals

If approved, pegcetacoplan will be the first and only treatment for patients with GA

- Slows GA progression with both every-other-month and monthly dosing, with effects increasing over time

- Safety data collected in real world population of over 1,200 patients with nearly 12,000 injections studied for 2 years

Pegcetacoplan binds to C3 and C3b inhibiting the downstream effects of the complement pathway



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
1258 patients at 232 sites in the combined studies

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
- 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

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

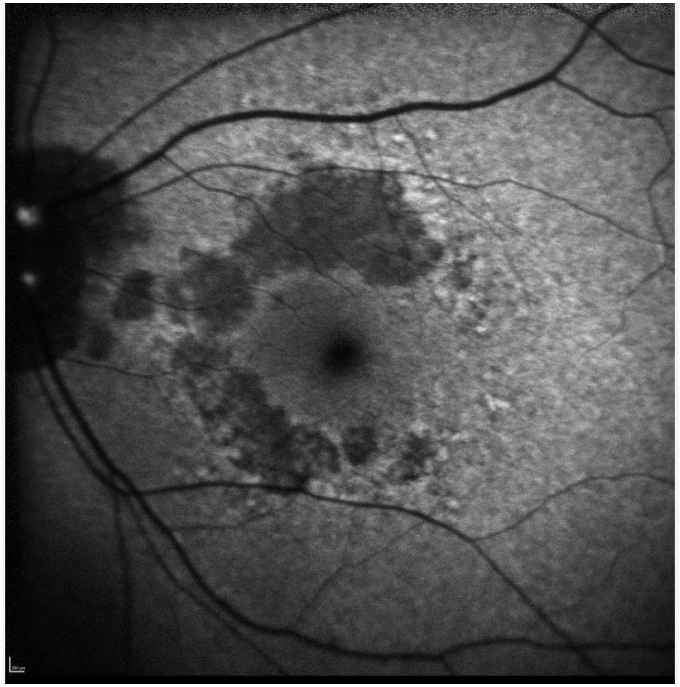
Characteristic	OAKS			DERBY		
	PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)	PM (N=201)	PEOM (N=201)	Sham Pooled (N=195)
Age, mean (SD)	78.8 (7.24)	78.1 (7.74)	78.6 (7.25)	78.7 (6.91)	79.2 (7.08)	78.6 (7.28)
Female, n (%)	125 (61.9%)	117 (57.1%)	133 (64.3%)	118 (58.7%)	120 (59.7%)	123 (63.1%)
Male, n (%)	77 (38.1%)	88 (42.9%)	74 (35.7%)	83 (41.3%)	81 (40.3%)	72 (36.9%)
Geographic region						
US, n (%)	147 (72.8%)	142 (69.3%)	148 (71.5%)	142 (70.6%)	122 (60.7%)	122 (62.6%)
ROW, n (%)	55 (27.2%)	63 (30.7%)	59 (28.5%)	59 (29.4%)	79 (39.3%)	73 (37.4%)
Caucasian, n (%)	185 (91.6%)	189 (92.2%)	188 (90.8%)	187 (93.0%)	186 (92.5%)	188 (96.4%)
GA lesion size (mm^2), mean (SD)	8.18 (3.895)	8.30 (3.904)	8.21 (3.712)	8.37 (4.181)	8.25 (3.894)	8.24 (4.261)
Square root GA lesion size (mm), mean (SD)	2.78 (0.682)	2.80 (0.674)	2.79 (0.647)	2.80 (0.722)	2.79 (0.678)	2.78 (0.734)
GA lesion size <7.5 mm^2, n (%)	101 (50.0%)	98 (47.8%)	104 (50.2%)	99 (49.3%)	98 (48.8%)	95 (48.7%)
Nonsubfoveal / extrafoveal lesion (location), n (%)	**86 (42.6%)**	**74 (36.1%)**	**60 (29.0%)**	**72 (35.8%)**	**81 (40.3%)**	**73 (37.4%)**
Unifocal lesion (focality), n (%)	59 (29.2%)	62 (30.2%)	68 (32.9%)	54 (26.9%)	53 (26.4%)	66 (33.8%)
Intermediate/large drusen >20, n (%)	93 (46.0%)	104 (50.7%)	104 (50.2%)	78 (38.8%)	78 (38.8%)	98 (50.3%)
NL-BCVA (ETDRS letters), mean (SD)	61.0 (15.30)	58.2 (17.03)	57.6 (16.59)	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.

GA lesion location affects GA growth rate

- Nonsubfoveal lesions grow more quickly than subfoveal lesions[1]

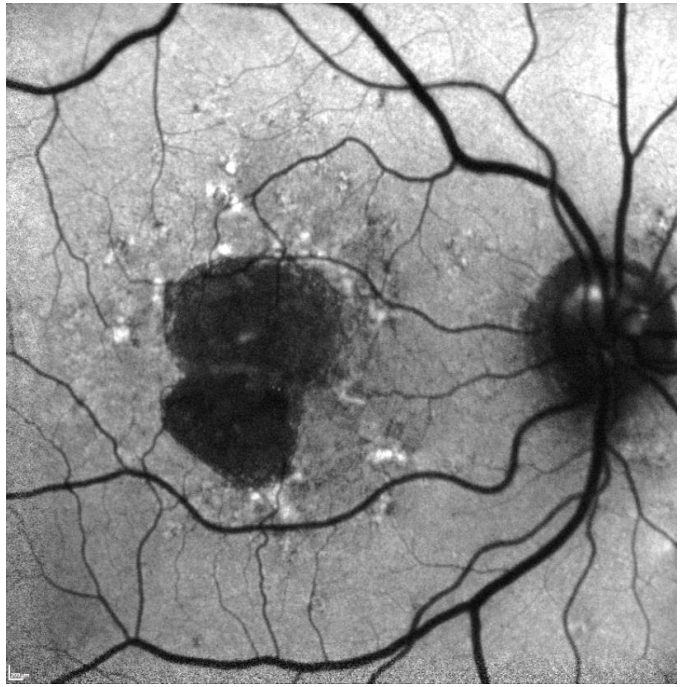
Nonsubfoveal



GA lesion border ≥ 1 micron from foveal center point

n=445; ~35% of OAKS and DERBY population

Subfoveal



GA lesion present at the center point of fovea

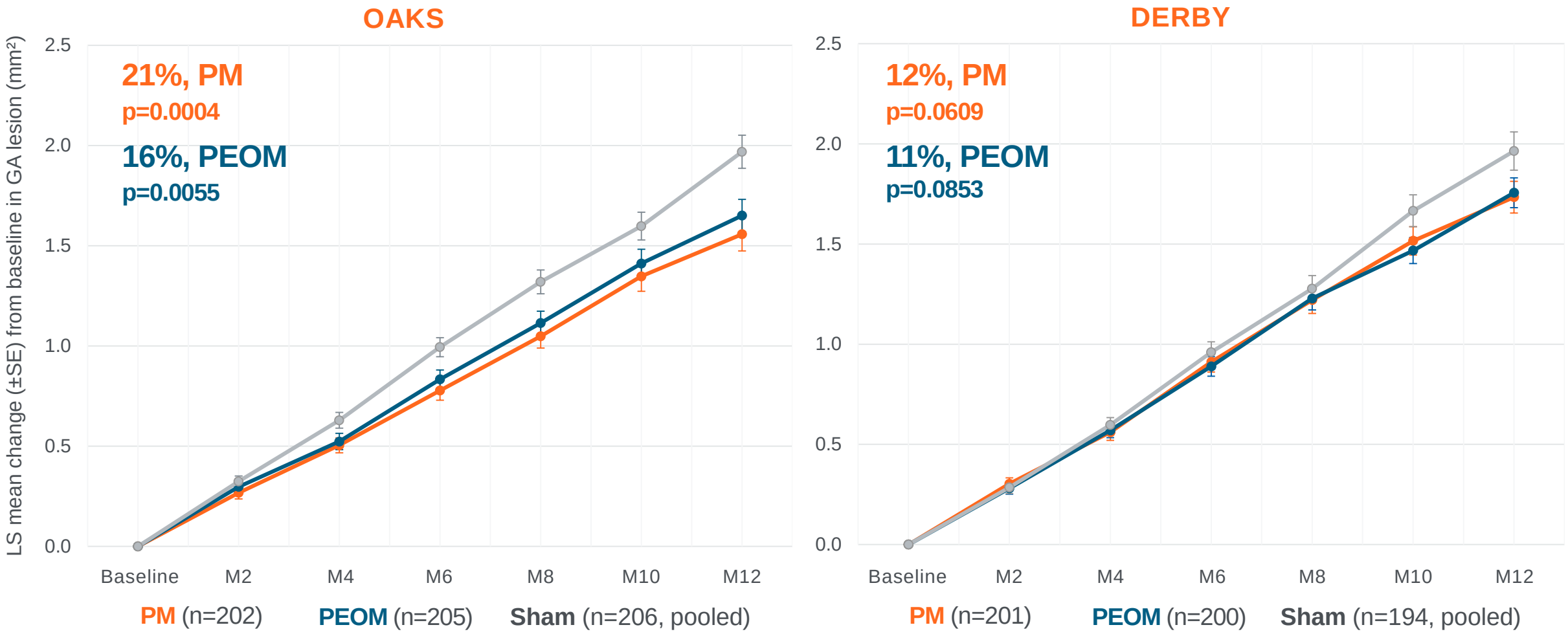
n=765; ~65% of OAKS and DERBY population

Images from OAKS and DERBY.

1. Fleckenstein M, et al. Ophthalmology 2018;125:369–90.

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

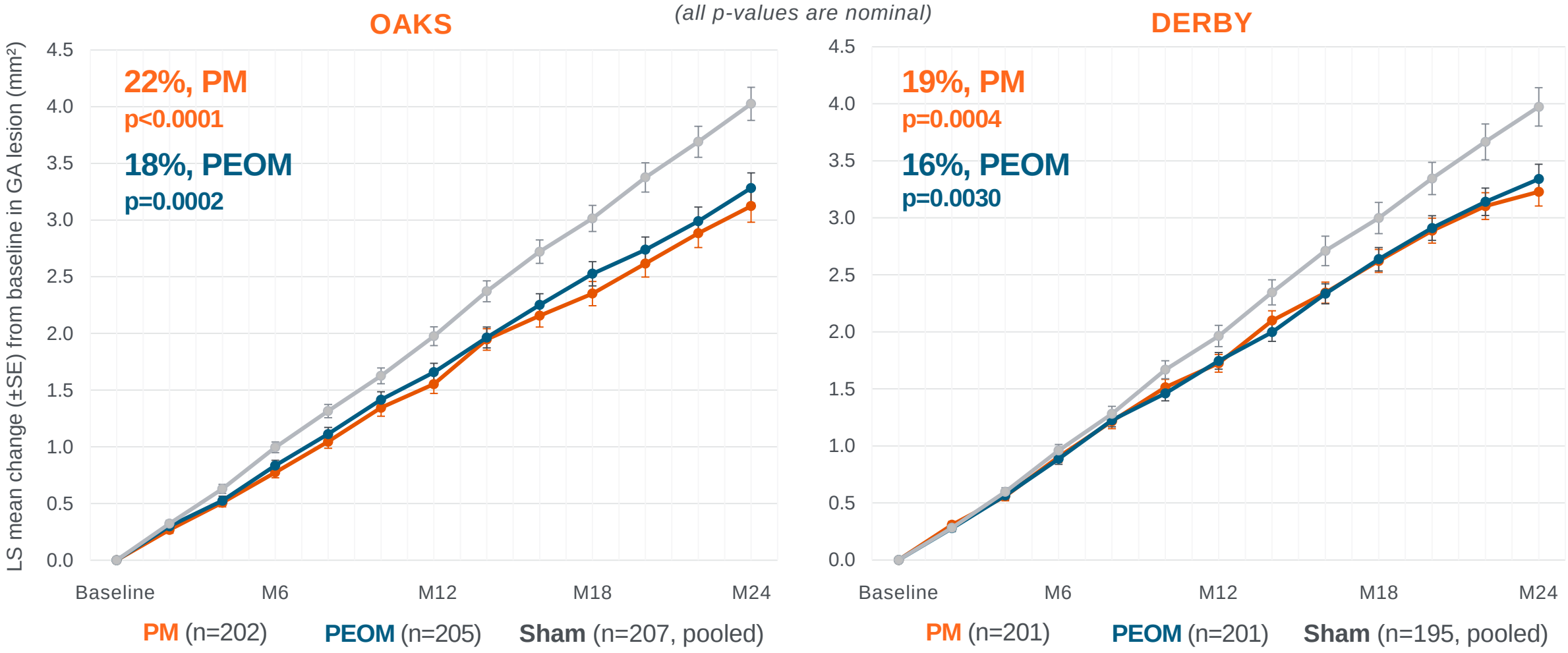
Reductions in GA lesion growth at Month 12



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.

Reductions in GA lesion growth at Month 24

(all p-values are nominal)



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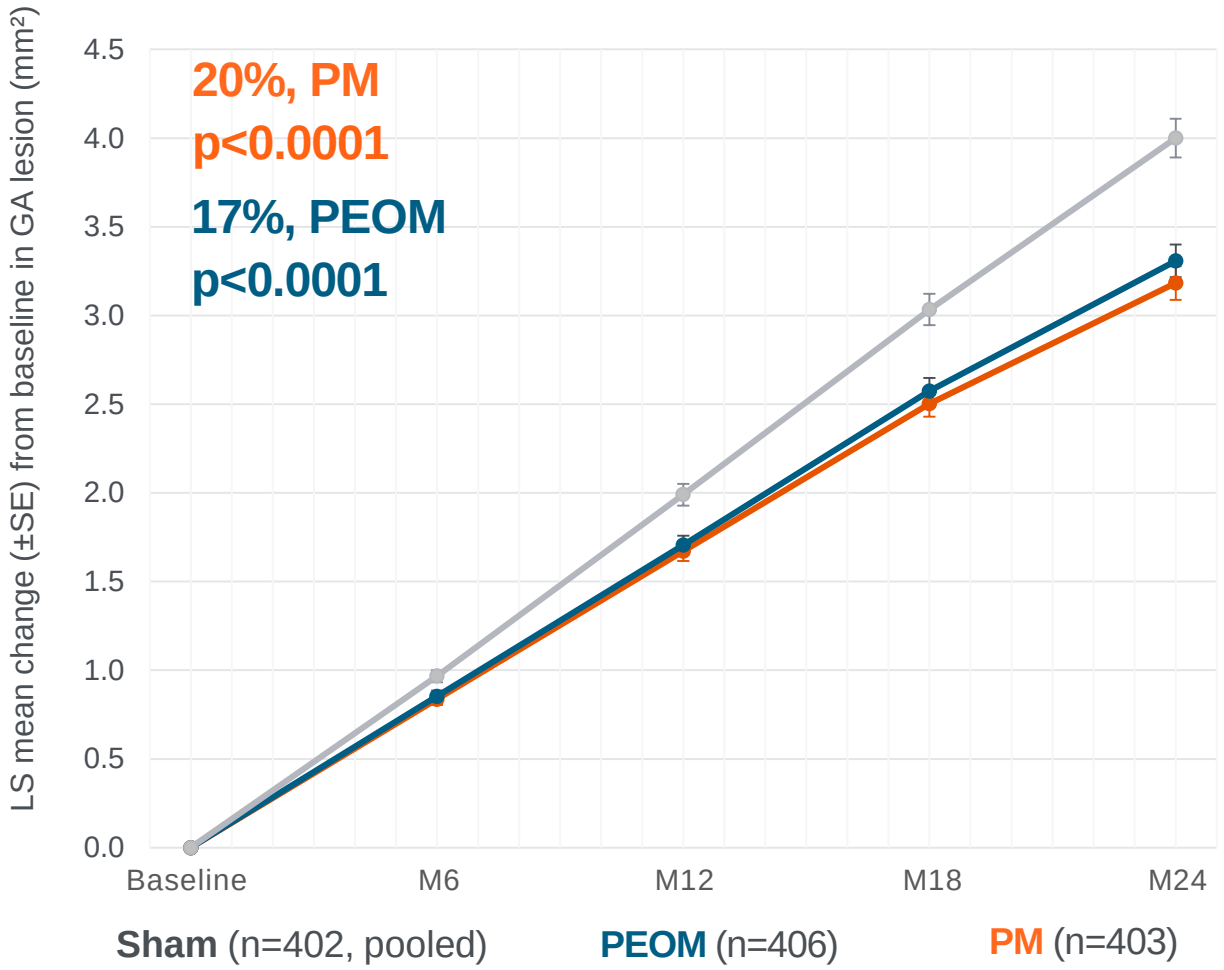
OAKS and DERBY combined

Piecewise linear slope analysis over 24 Months

(all p-values are nominal)



Increased treatment effect over Months 18-24:

- **PM: 30%**
- **PEOM: 24%**

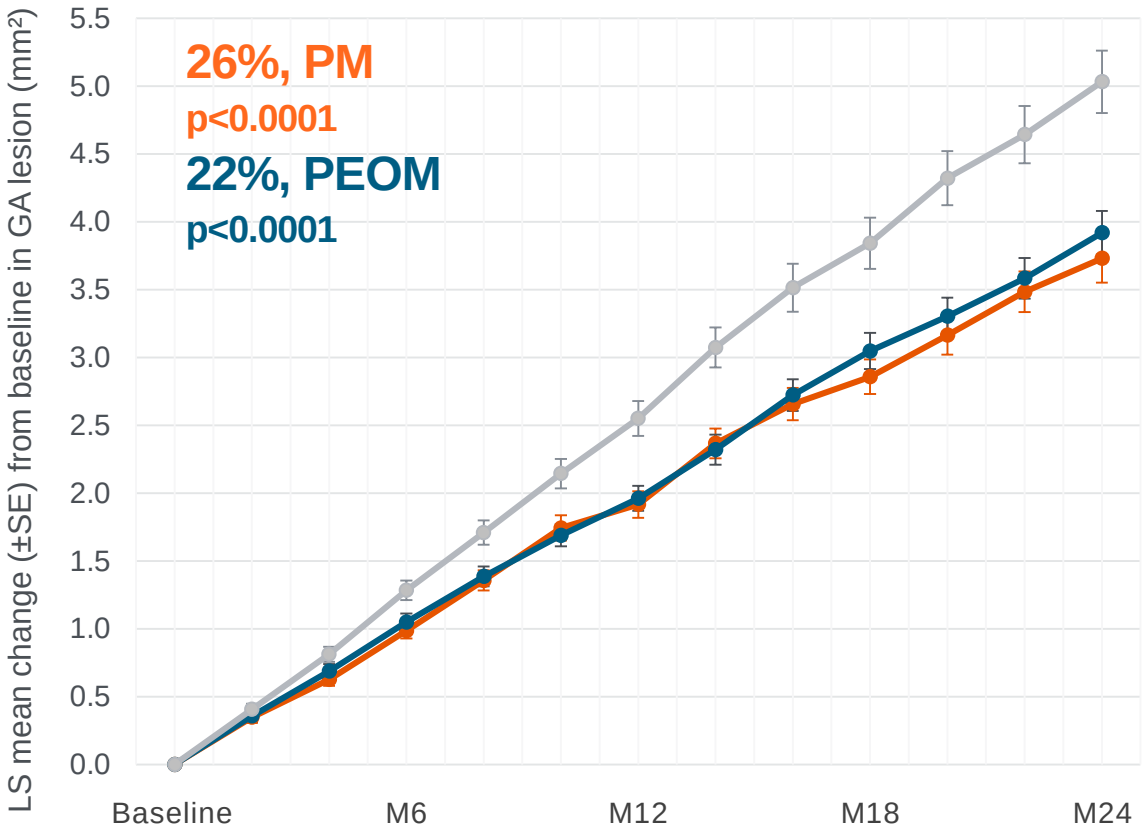
LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 24, with knots at Months 6, 12 & 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments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

OAKS and DERBY combined / pre-specified analysis

Reductions in GA lesion growth by lesion location

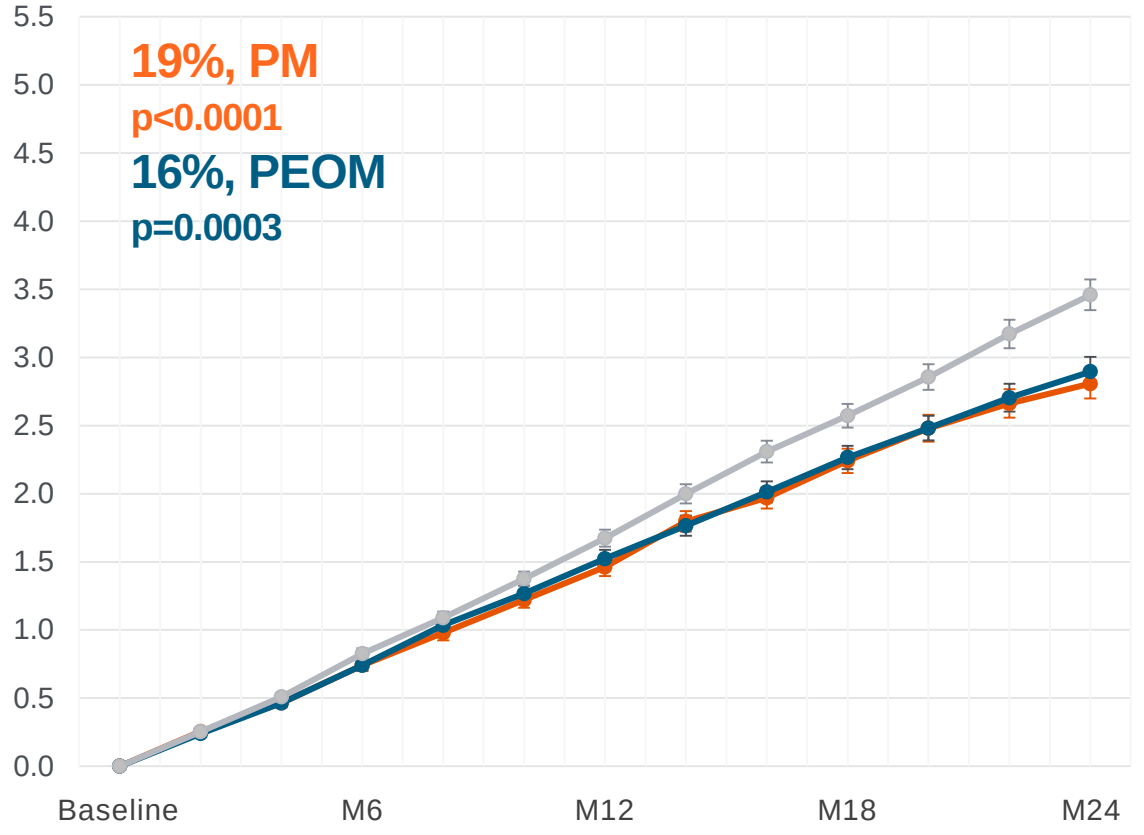
Nonsubfoveal

(all p-values are nominal)



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

Subfoveal

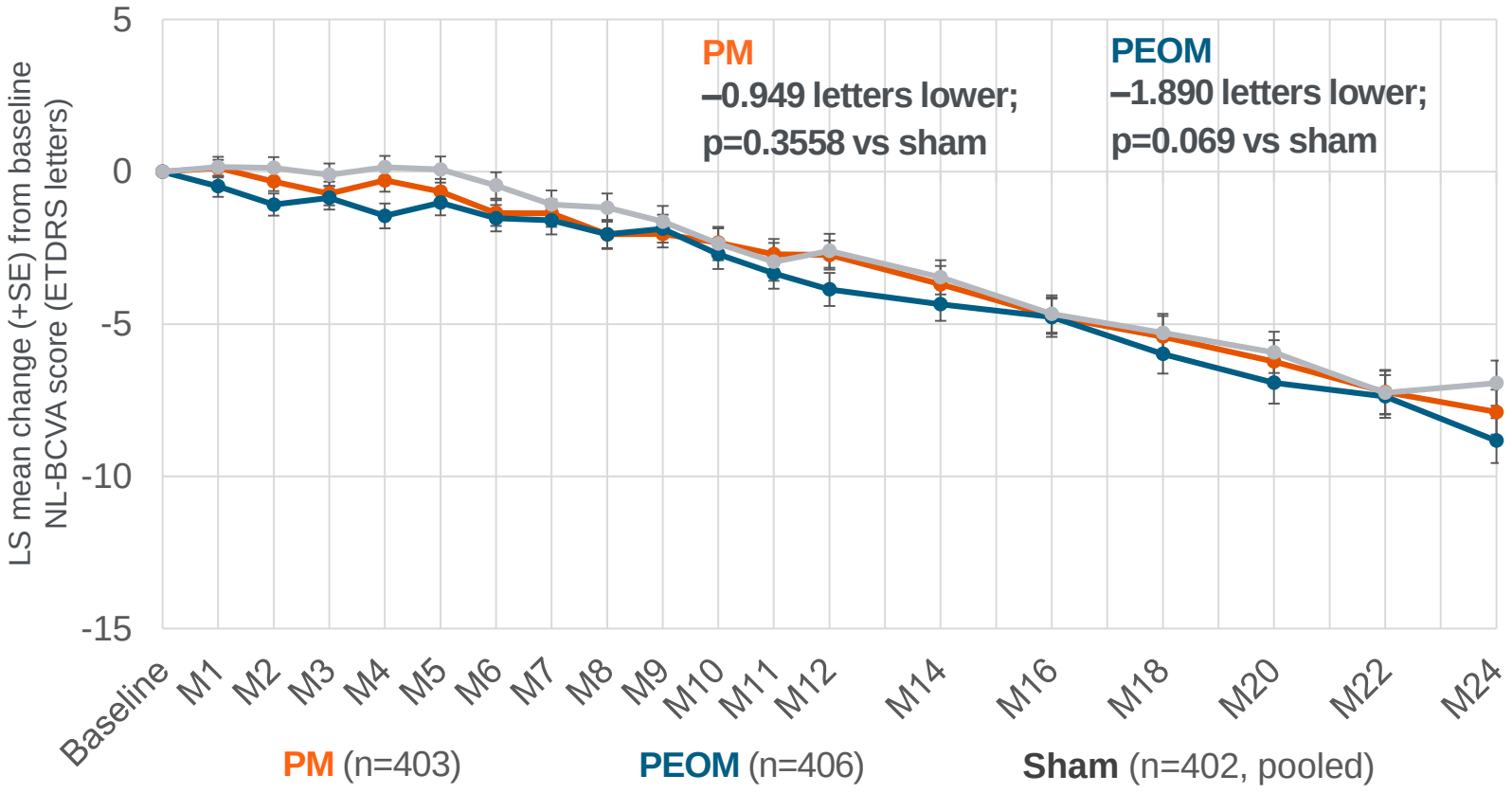


PM (n=245) **PEOM** (n=251) **Sham** (n=269, pooled)

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

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

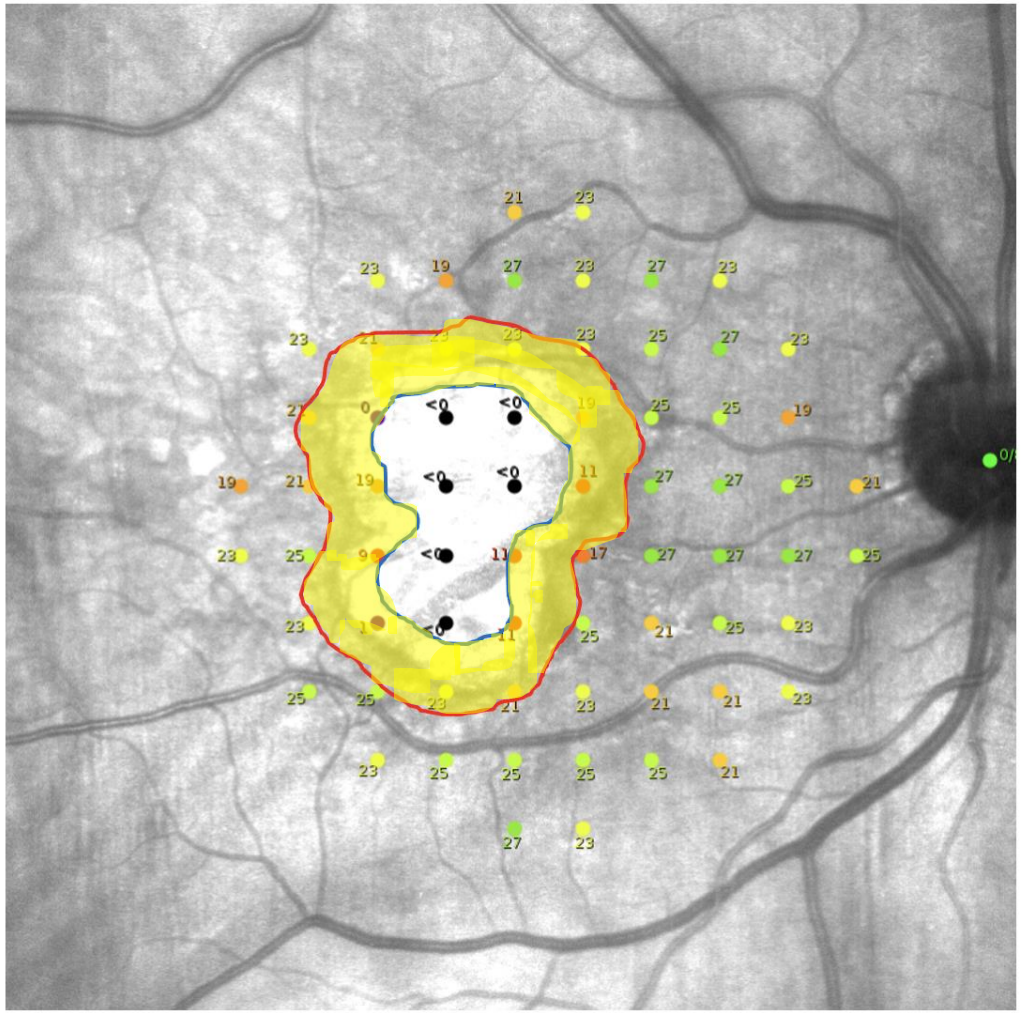
- BCVA
- Maximum reading speed
- Functional Reading Independence Index
- Microperimetry: Mean threshold sensitivity (OAKS only)

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.

Microperimetry: post hoc analysis of the junctional zone

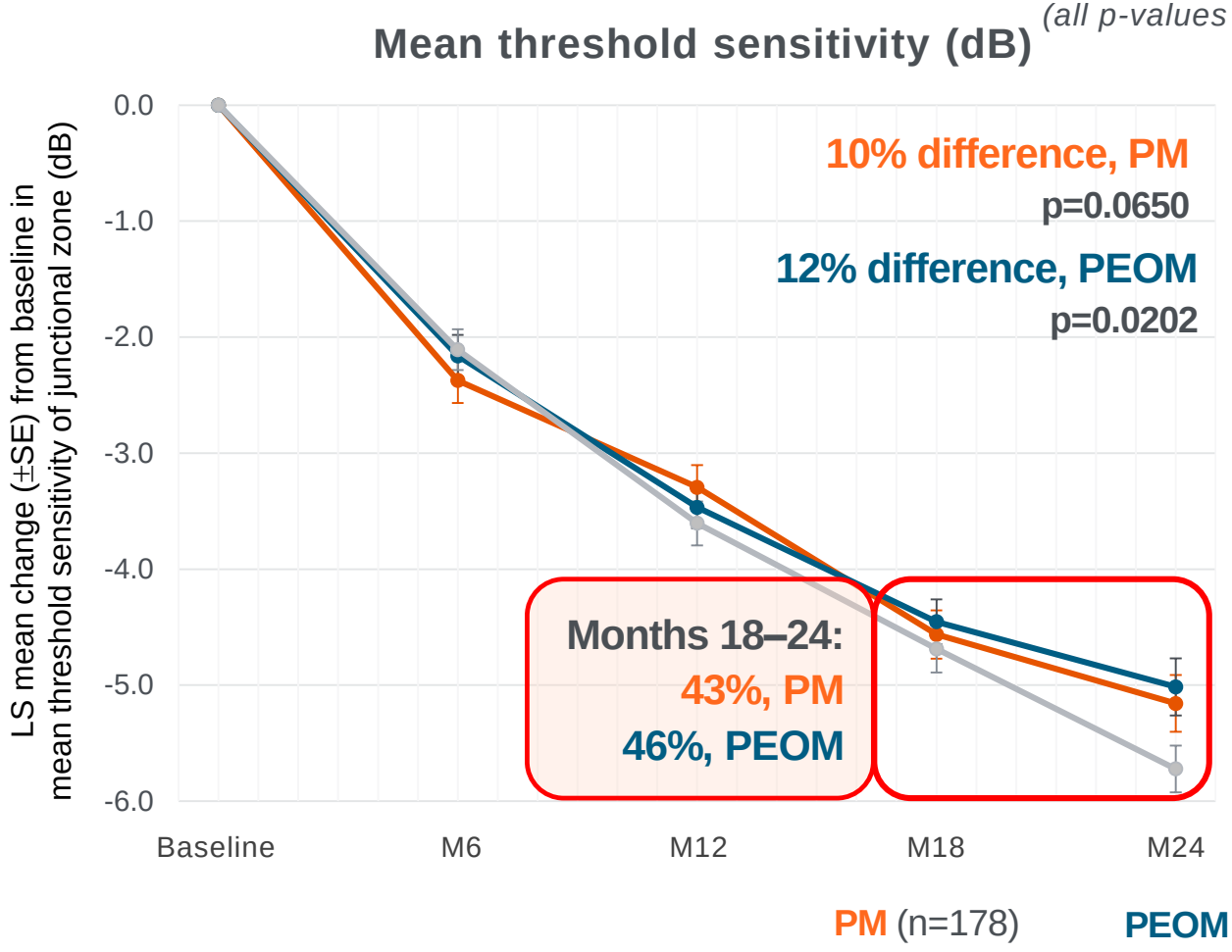
- Hypothesis: linear expansion of GA lesions of ~100–150 microns/year[1] means that pegcetacoplan preservation of retinal tissue may primarily be reflected in preserved photoreceptor function in retina near GA lesion borders at baseline
- Junctional zone (area within 250 microns of each side of GA lesion border) was created on FAF for each patient
- Microperimetry endpoints were assessed within this region[a]

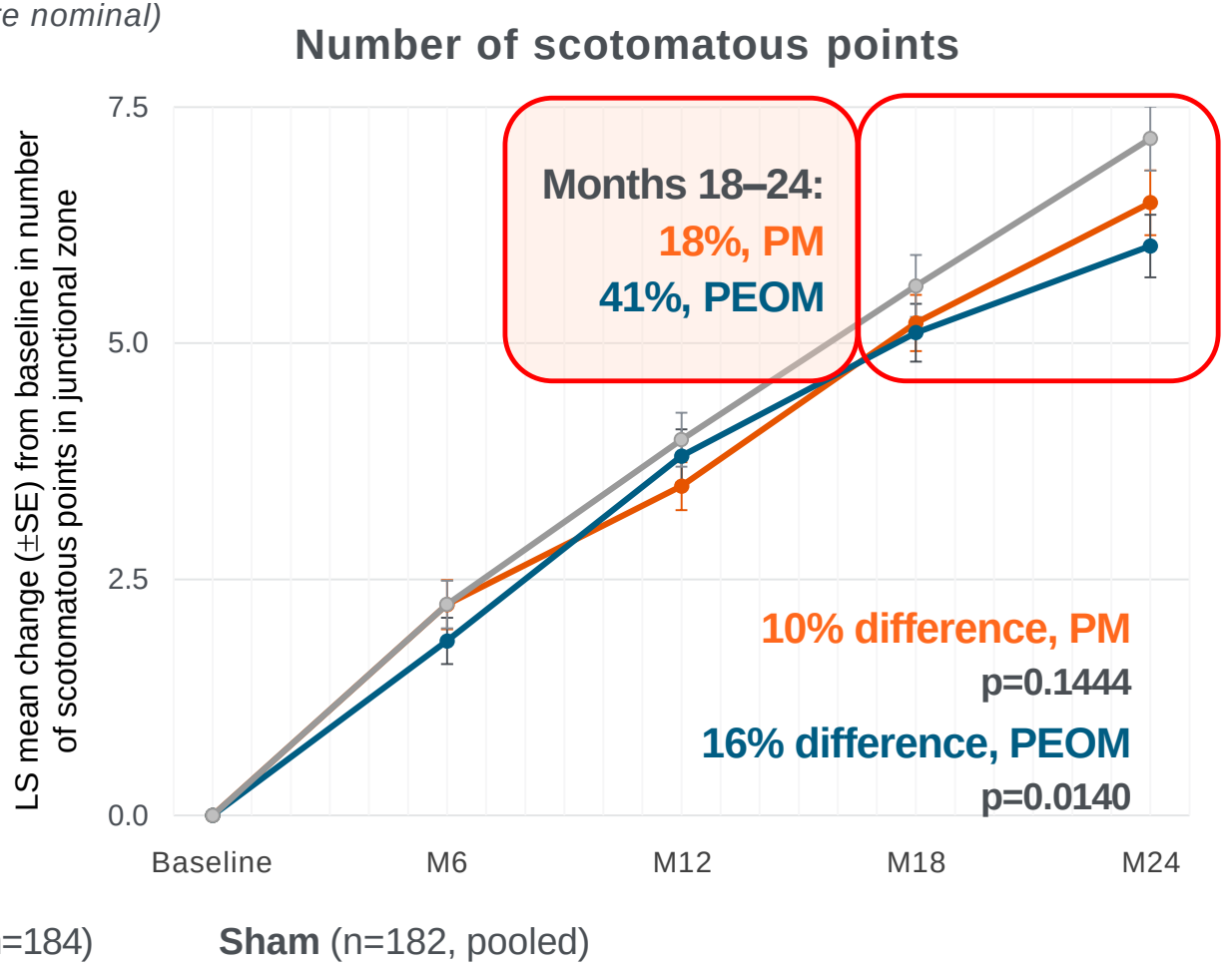


[1]Shen L et al. *Ophthalmol Retina* 2020;4:899–910.
[a]68 spots on grid.
FAF=fundus autofluorescence; GA=geographic atrophy.

Microperimetry junctional zone analysis (post-hoc)
Signal of functional preservation with pegcetacoplan treatment

(all p-values are nominal)



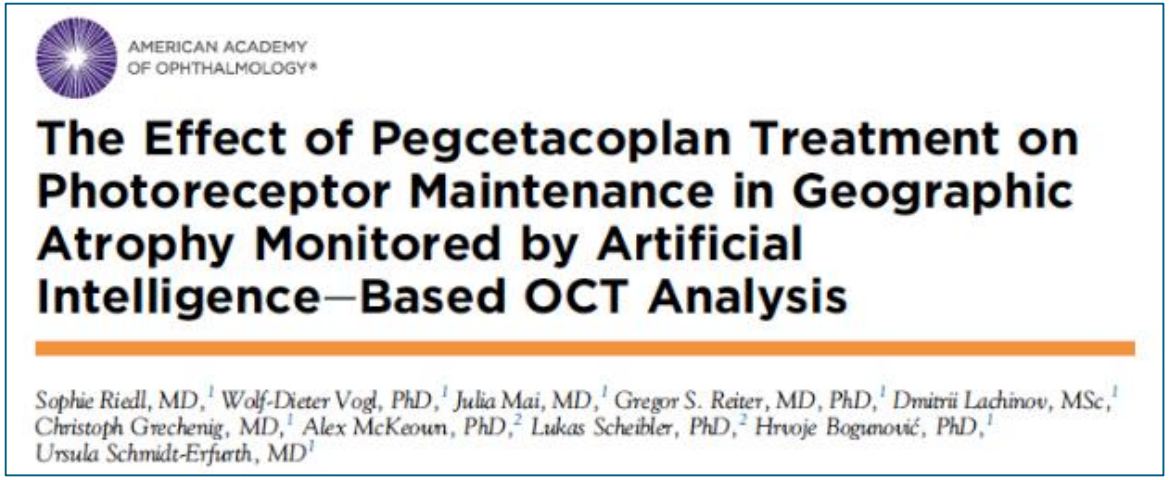


PM (n=178) **PEOM** (n=184) **Sham** (n=182, pooled)

LS means estimated from an MMRM. Subjects in the mITT population who had a baseline and at least one post-baseline value for junctional zone mean threshold sensitivity or junctional zone number of scotomatous points were included in the analysis. Junctional zone defined as –250 µm inside baseline atrophy border to +250 µm outside atrophy border. dB=decibel; 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.

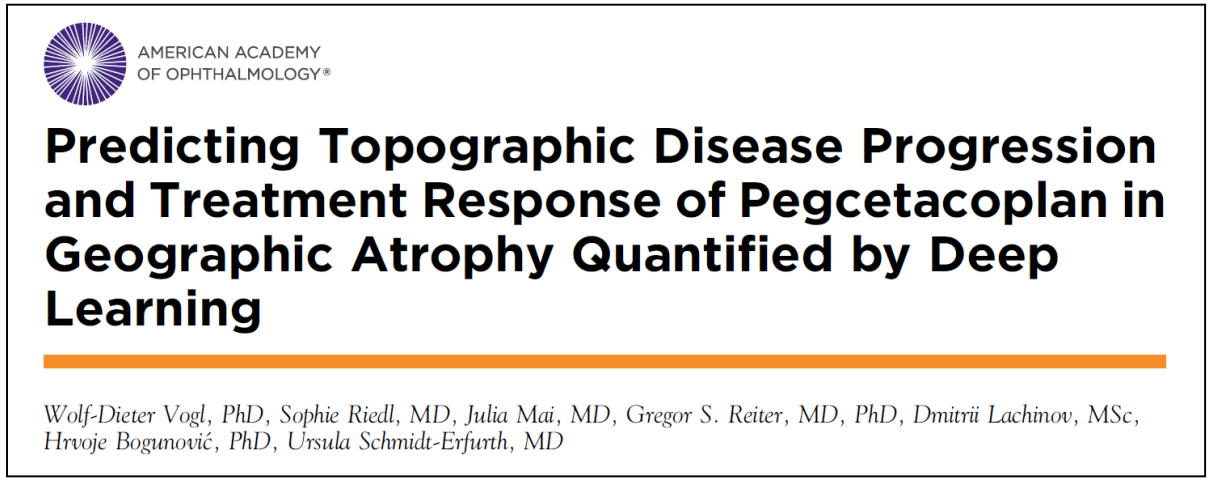
Methodology of Photoreceptor and RPE loss analysis

- Exploratory *post hoc* analysis of OAKS/DERBY at 12 months using AI-based automated segmentation to map PR and RPE layers
- Analysis of OCT images from SPECTRALIS ® machines by Schmidt-Erfurth et al.


AMERICAN ACADEMY OF OPHTHALMOLOGY®

The Effect of Pegcetacoplan Treatment on Photoreceptor Maintenance in Geographic Atrophy Monitored by Artificial Intelligence–Based OCT Analysis

Sophie Riedl, MD,[1] Wolf-Dieter Vogl, PhD,[1] Julia Mai, MD,[1] Gregor S. Reiter, MD, PhD,[1] Dmitrii Lachinov, MSc,[1] Christoph Grechenig, MD,[1] Alex McKeown, PhD,[2] Lukas Scheibler, PhD,[2] Hrvoje Bogunović, PhD,[1] Ursula Schmidt-Erfurth, MD[1]


AMERICAN ACADEMY OF OPHTHALMOLOGY®

Predicting Topographic Disease Progression and Treatment Response of Pegcetacoplan in Geographic Atrophy Quantified by Deep Learning

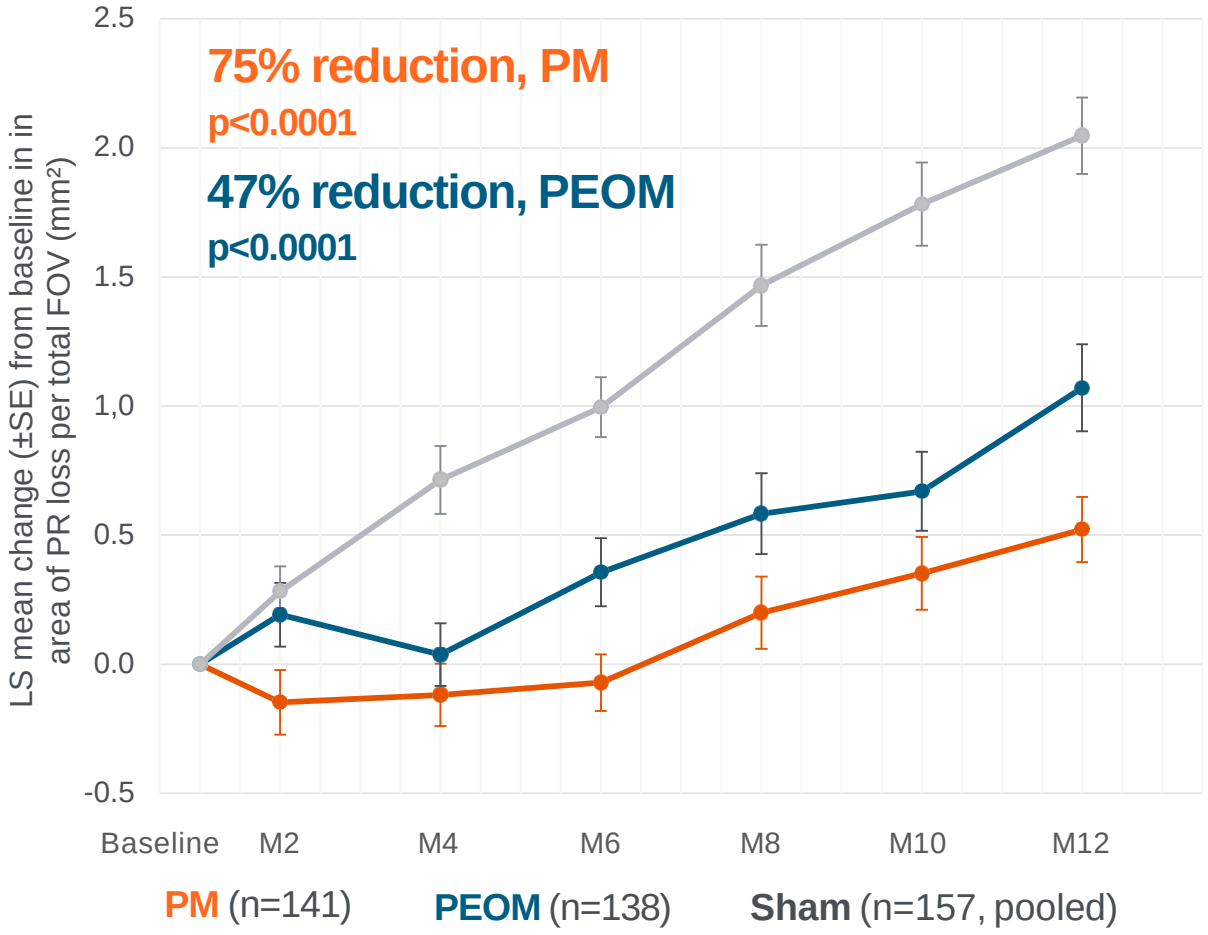
Wolf-Dieter Vogl, PhD, Sophie Riedl, MD, Julia Mai, MD, Gregor S. Reiter, MD, PhD, Dmitrii Lachinov, MSc, Hrvoje Bogunović, PhD, Ursula Schmidt-Erfurth, MD

1. Orlando JI, et al. *Sci Rep* 2020;10:5619. 2. Lachinov D, et al. Presentation at Association for Research in Vision and Ophthalmology (ARVO) 2021.
2D=two-dimensional; 3D=three-dimensional; PR=photoreceptor; RPE=retinal pigmented epithelium.

Reduction in photoreceptor and RPE loss at Month 12

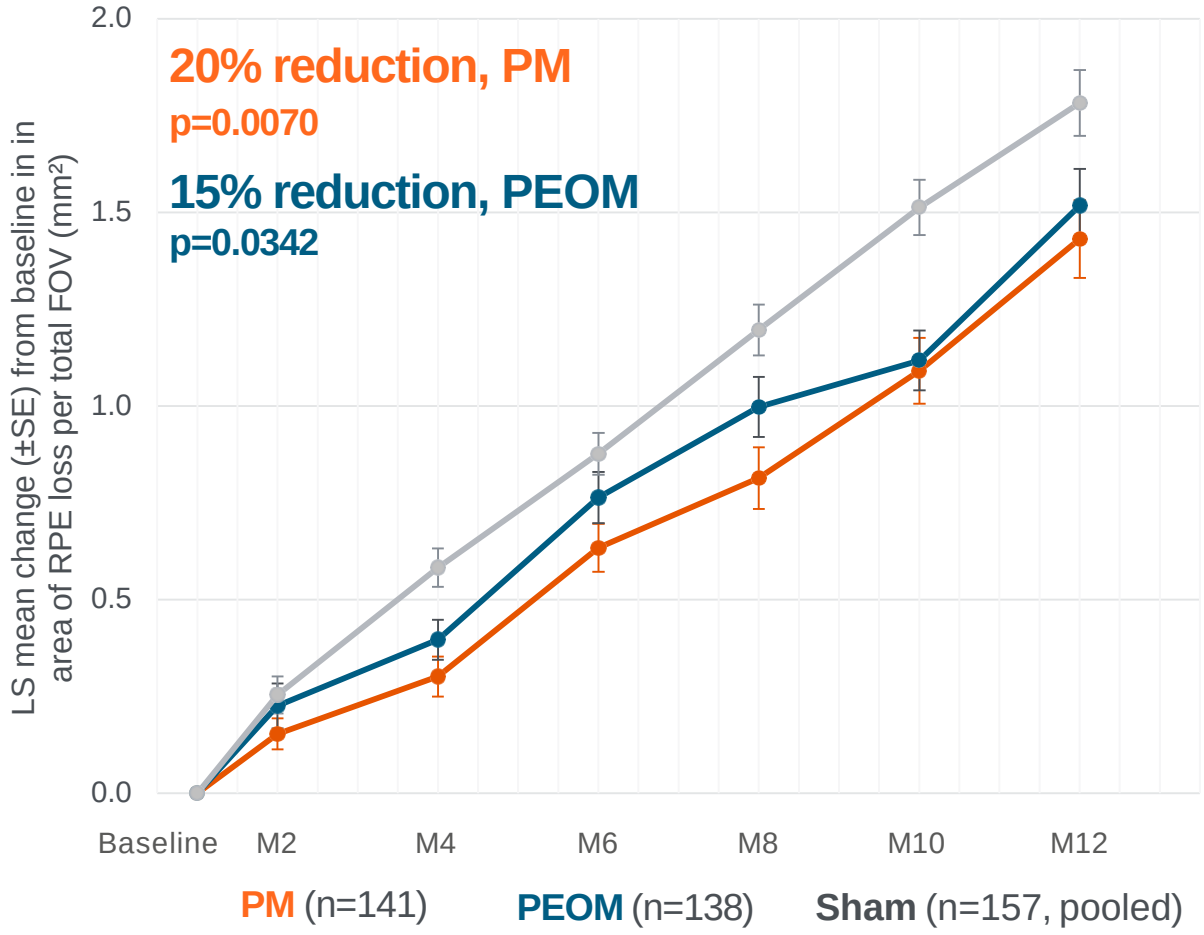
(all p-values are nominal)

Photoreceptor loss



PM (n=141) **PEOM** (n=138) **Sham** (n=157, pooled)

RPE loss



PM (n=141) **PEOM** (n=138) **Sham** (n=157, pooled)

Analysis only included patients with OCT images from SPECTRALIS® machines.

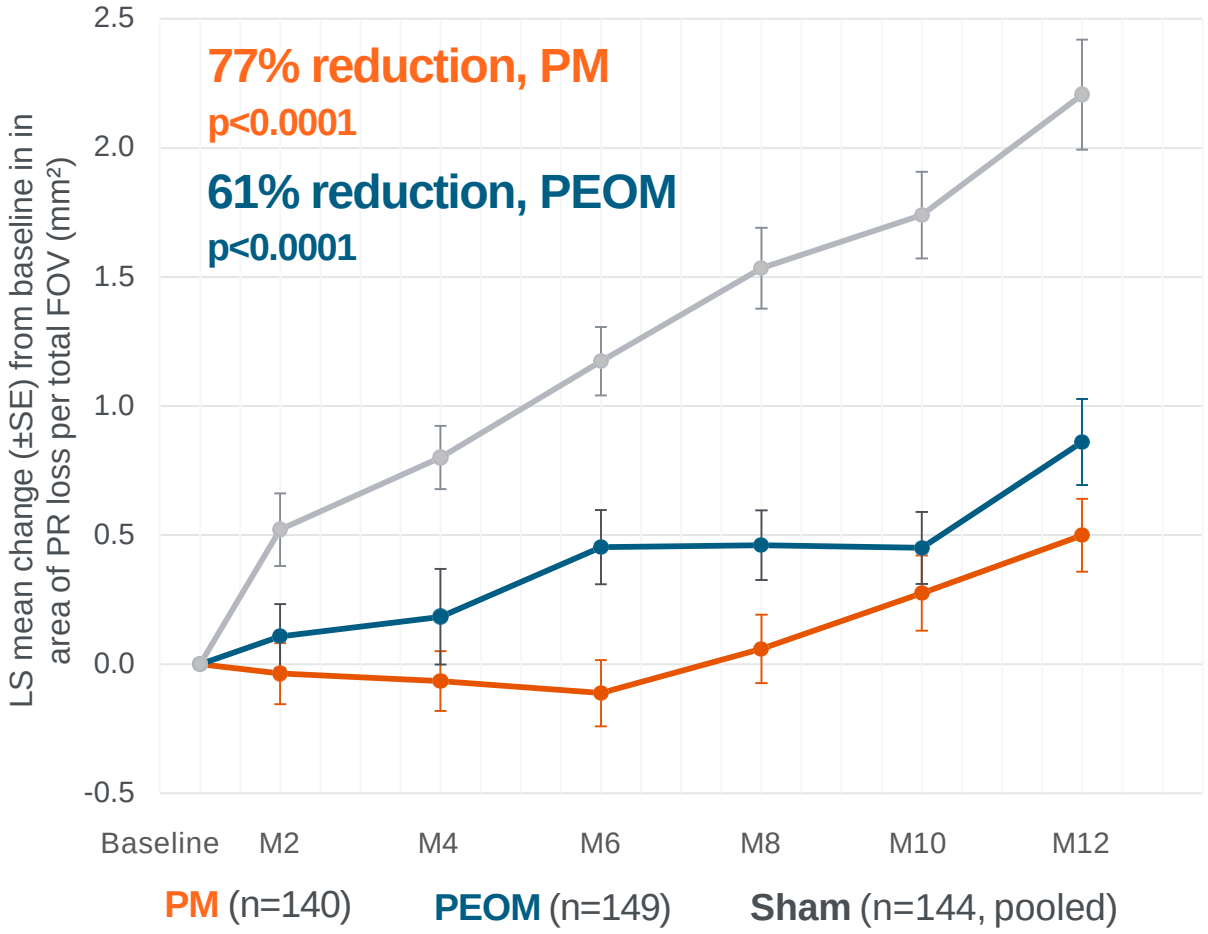
LS means estimated from MMRM analysis. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.

LS=least square; FOV=field of vision; M=month; mITT=modified intent-to-treat; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; PR=photoreceptor; RPE=retinal pigmented epithelium; SE=standard error.

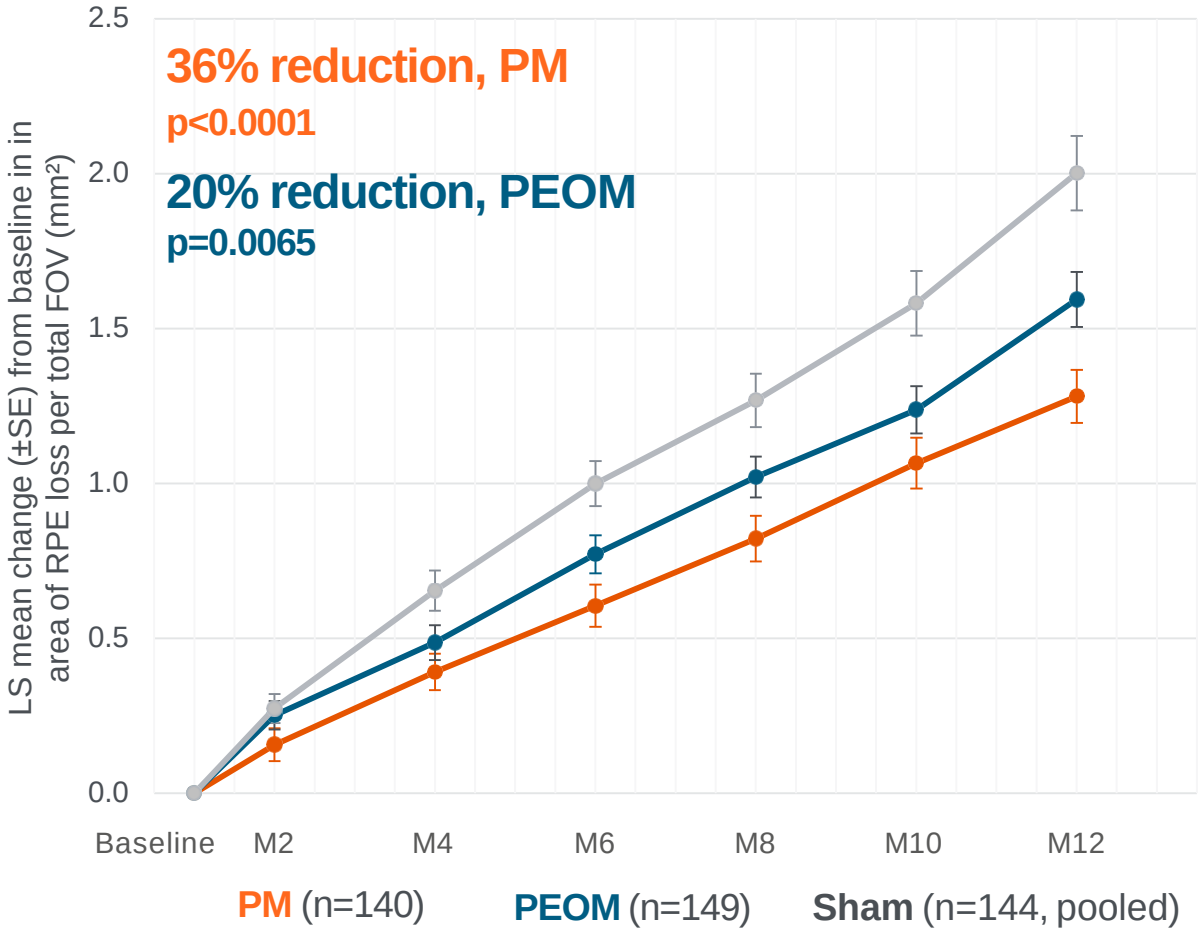
Reduction in photoreceptor and RPE loss at Month 12

(all p-values are nominal)

Photoreceptor loss



RPE loss



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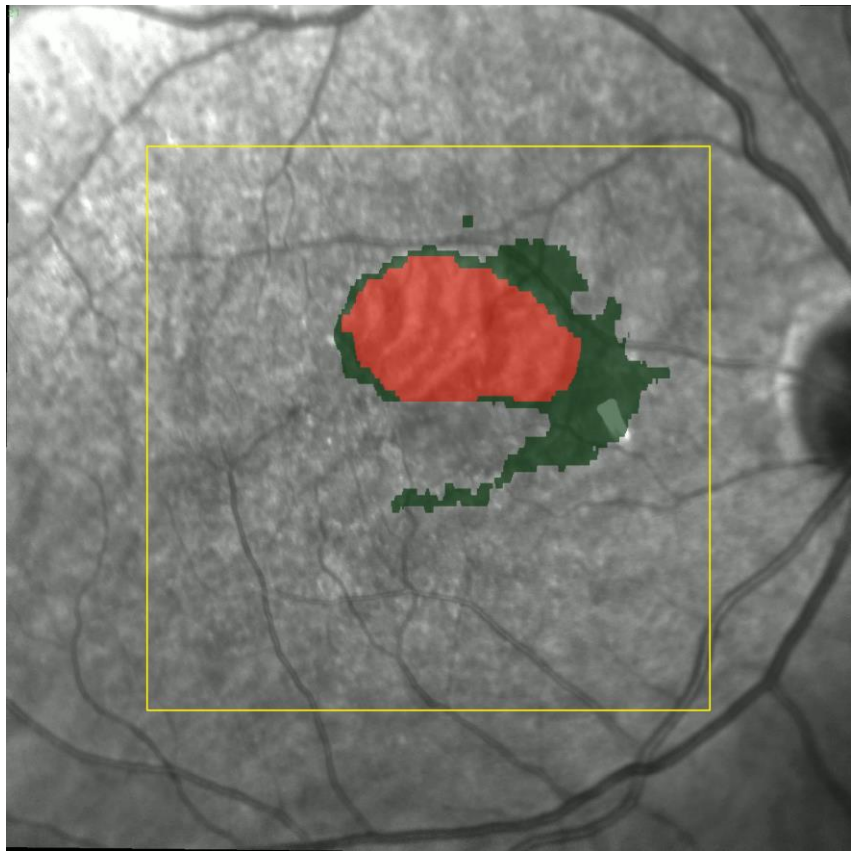
Photoreceptor and RPE loss in a pegcetacoplan-treated study eye vs. an untreated fellow eye over 12 months in the Phase 3 trials

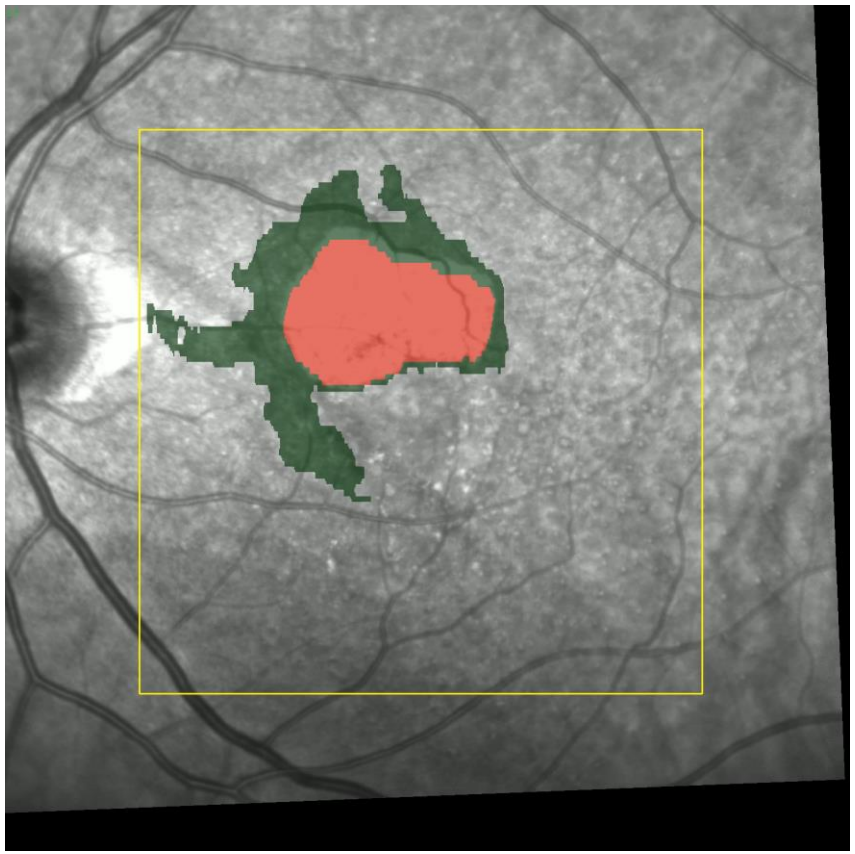
Study Eye



PR loss

RPE loss

Fellow Eye



Area of RPE loss grew by ~50% in the treated eye and by ~225% in the fellow eye at one

PR=photoreceptor; RPE=retinal pigmented epithelium.

RetInSight AI to Eye

If approved, pegcetacoplan will be the first and only treatment for patients with GA

- Slows GA progression with both every-other-month and monthly dosing, with effects increasing over time

- Safety data collected in real world population of over 1,200 patients with nearly 12,000 injections studied for 2 years

GA=geographic atrophy