Pegcetacoplan in Geographic Atrophy: 24-Month Efficacy Results From the Phase 3 OAKS and DERBY Trials – Impact on Retinal Cells

Sunir Garg

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Disclosures

- Sunir Garg has the following financial interests or relationships to disclose
    - Consultant/advisor for Allergan, Apellis, Bausch and Lomb, Boehringer Ingelheim, Kanaph, and Merck Manual
    - Leadership or fiduciary role in the American Society of Retina Specialists
    - Receipt of grant or contract from the American Academy of Ophthalmology
    - Receipt of honoraria from Genentech
    - Receipt of research funding from Apellis, Boehringer Ingelheim, Genentech, and NGM Bio
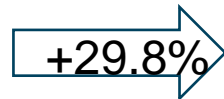
Introduction

- Geographic atrophy can result in poor vision
- Complement plays an important role
- Pegcetacoplan slows the rate of atrophy
- Slowing atrophy can result in better preservation of RPE cells
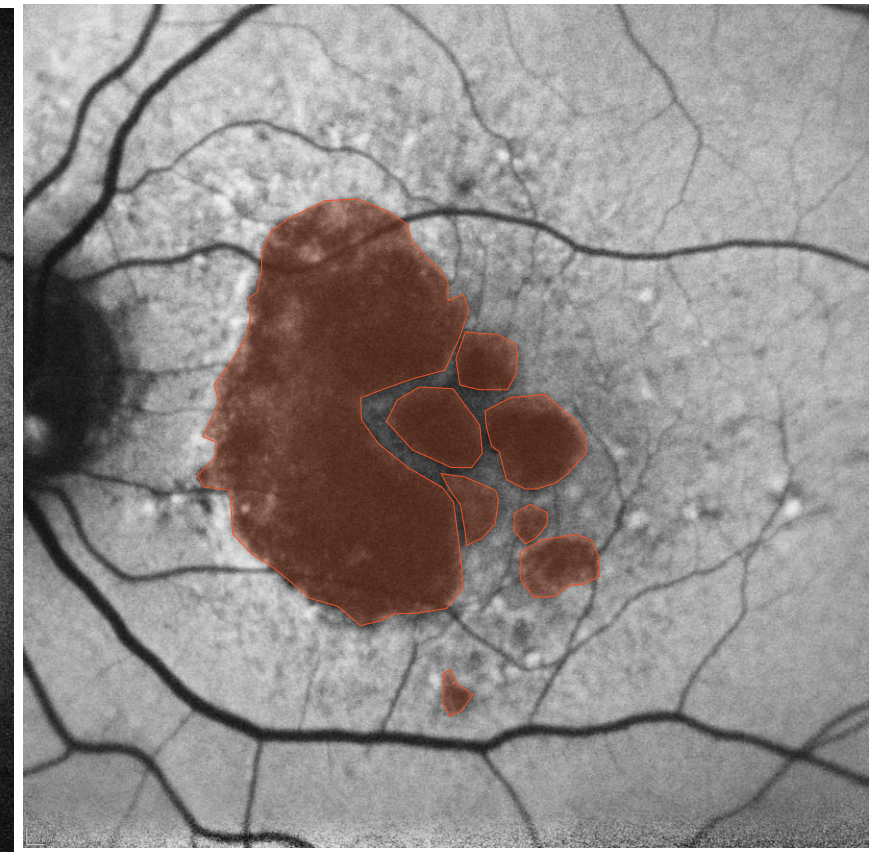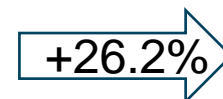
GA progression over 2 years
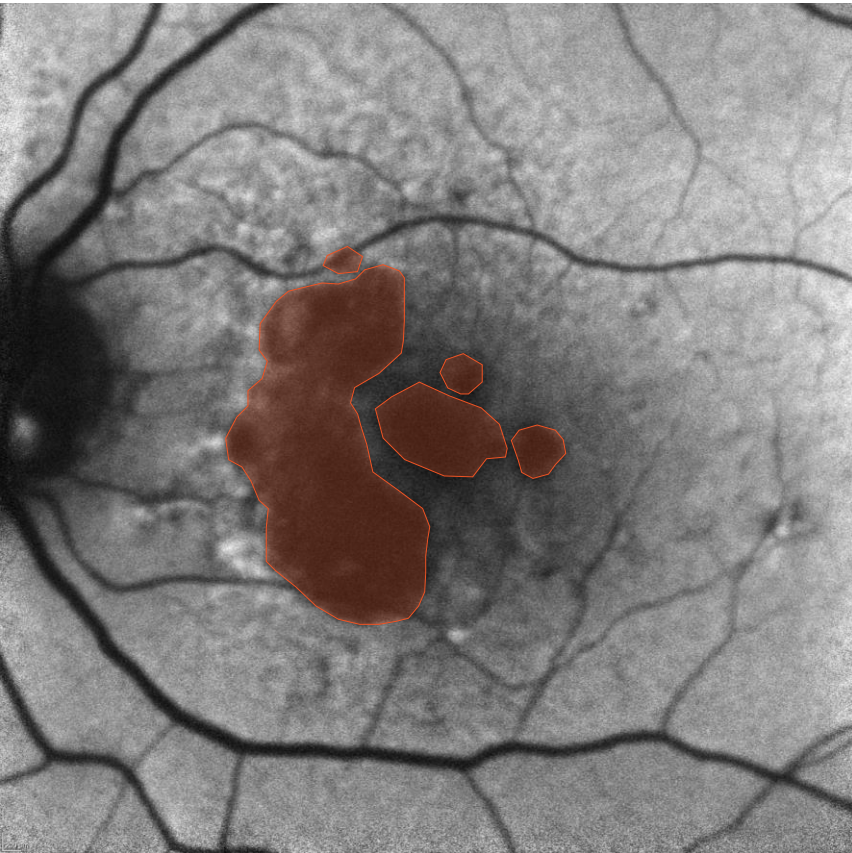
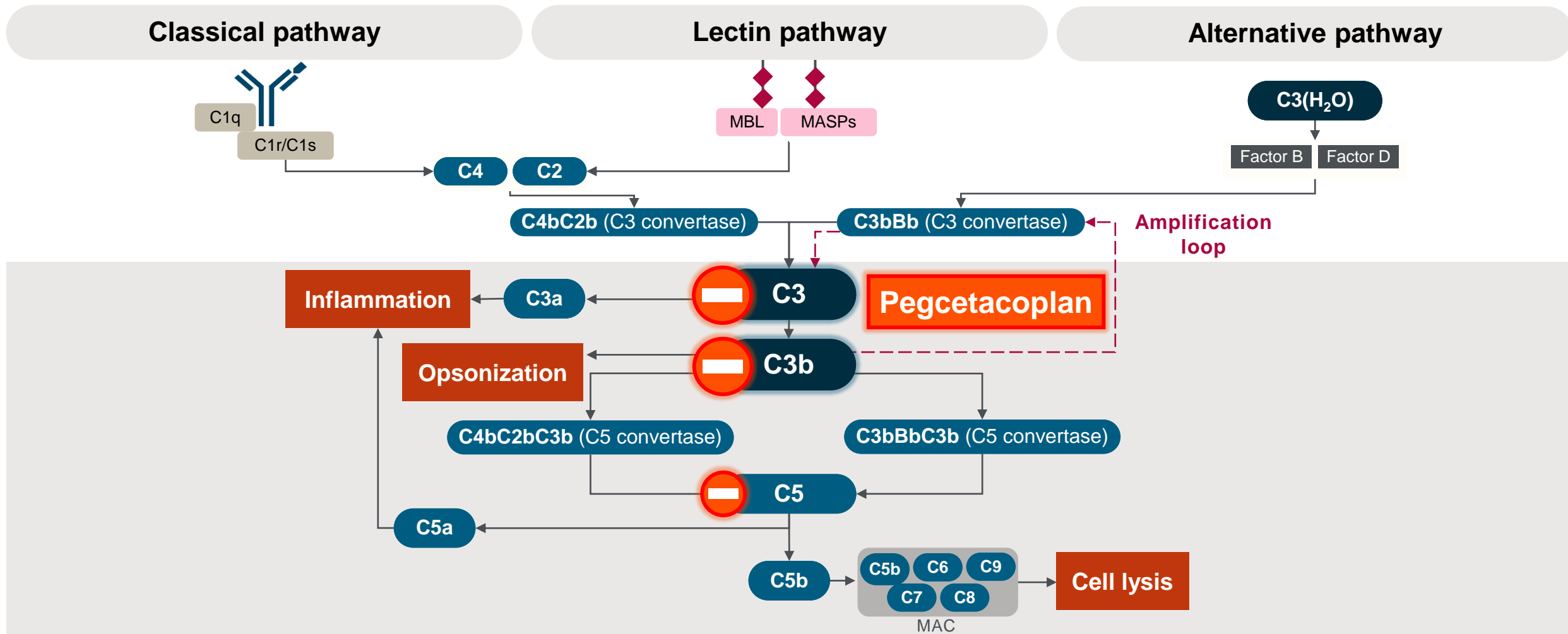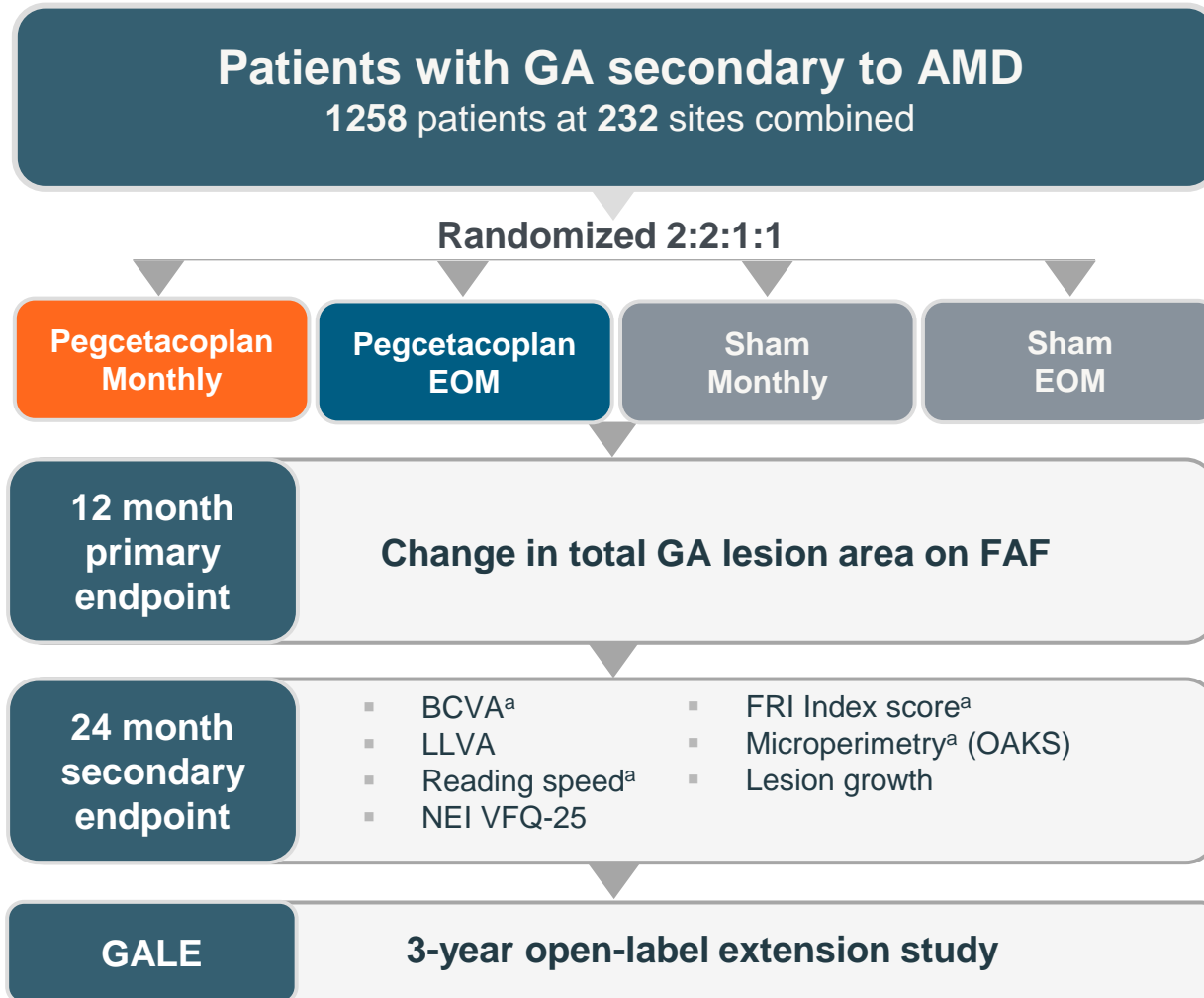| Baseline		13M		24M
Total area= 6.35 mm^2	+29.8% →	Total area= 8.24 mm^2	+26.2% →	Total area= 10.39 mm^2

Pegcetacoplan binds to C3 and C3b regulating the overactive complement system

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.

Phase 3 OAKS and DERBY trials: Design and key criteria

Patients with GA secondary to AMD
1258 patients at **232** sites combined

Randomized 2:2:1:1

Pegcetacoplan Monthly	Pegcetacoplan EOM	Sham Monthly	Sham EOM

12 month primary endpoint — Change in total GA lesion area on FAF

24 month secondary endpoint
- BCVA[a]
- LLVA
- Reading speed[a]
- NEI VFQ-25
- FRI Index score[a]
- Microperimetry[a] (OAKS)
- Lesion growth

GALE — **3-year open-label extension study**

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; If multifocal, at least 1 focal lesion must be ≥1.25 mm^2 (0.5 DA)
  - Presence of perilesional hyperautofluorescence
  - **GA lesions with or without subfoveal involvement allowed**

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)

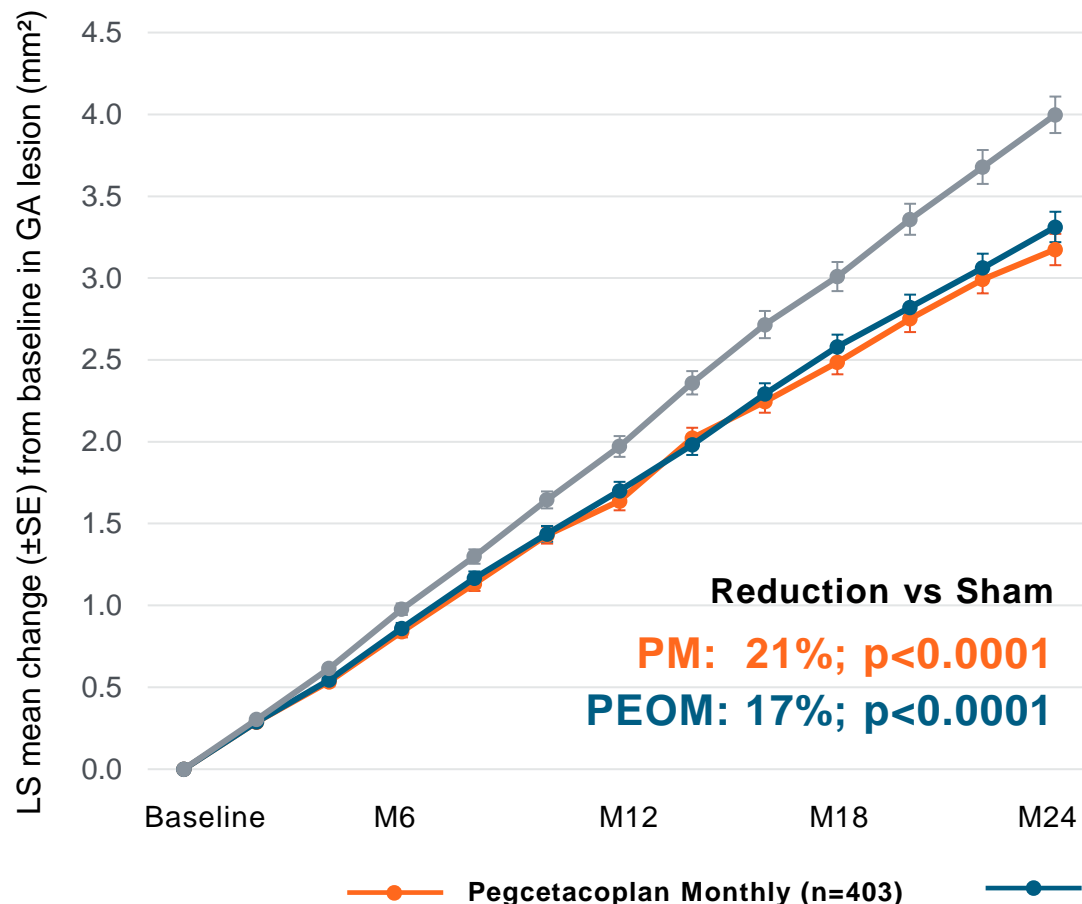**CNV in the fellow eye was not exclusionary**

OAKS and DERBY combined
Reductions in GA lesion growth at Month 24

(all p-values are nominal)

MMRM primary analysis

Piecewise linear slope analysis

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

Reduction vs Sham
PM: 21%; p<0.0001
PEOM: 17%; p<0.0001

Reduction vs Sham
PM: 20%; p<0.0001
PEOM: 17%; p<0.0001

— Pegcetacoplan Monthly (n=403)   — Pegcetacoplan EOM (n=406)   — Sham (n=402)
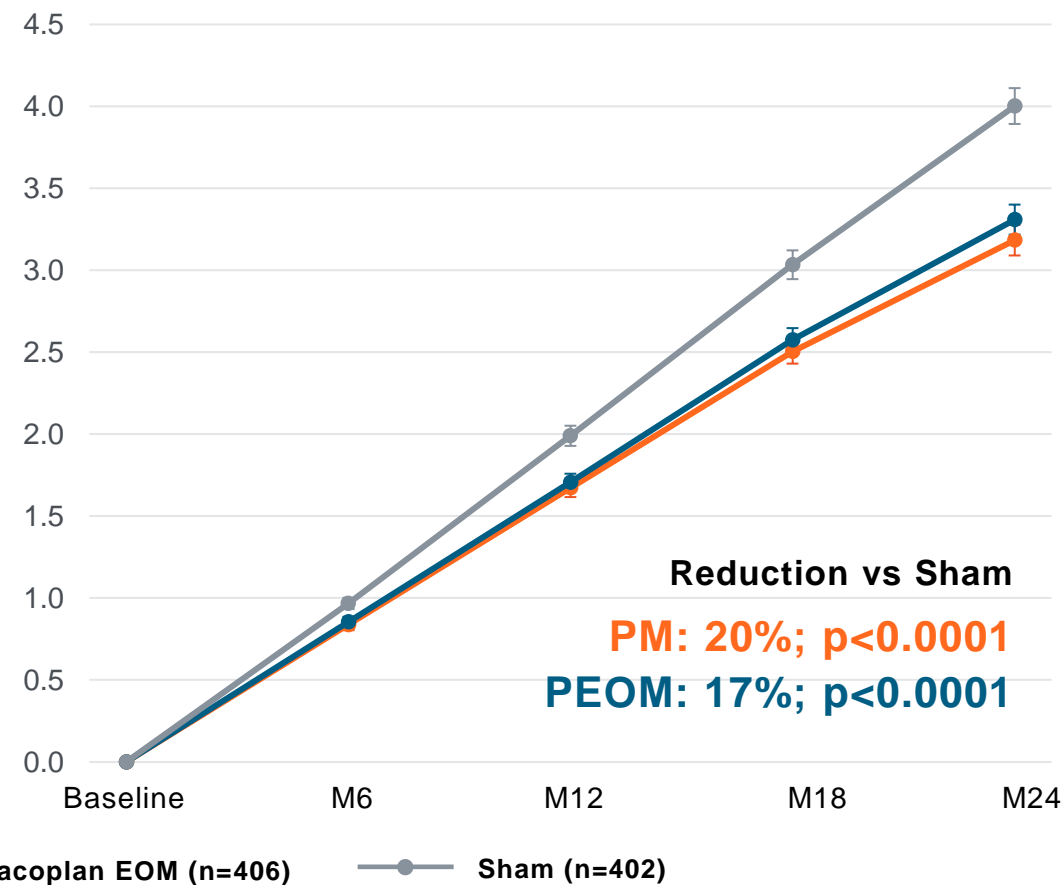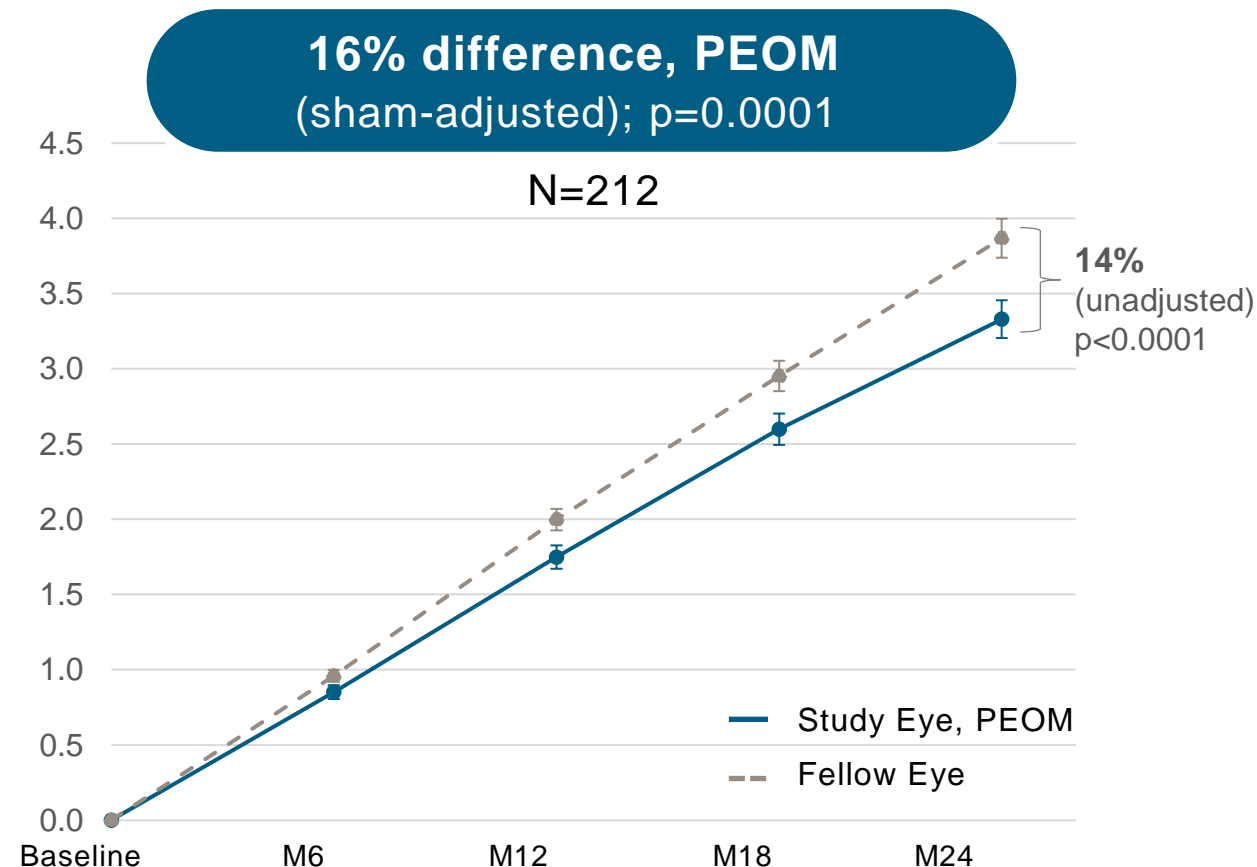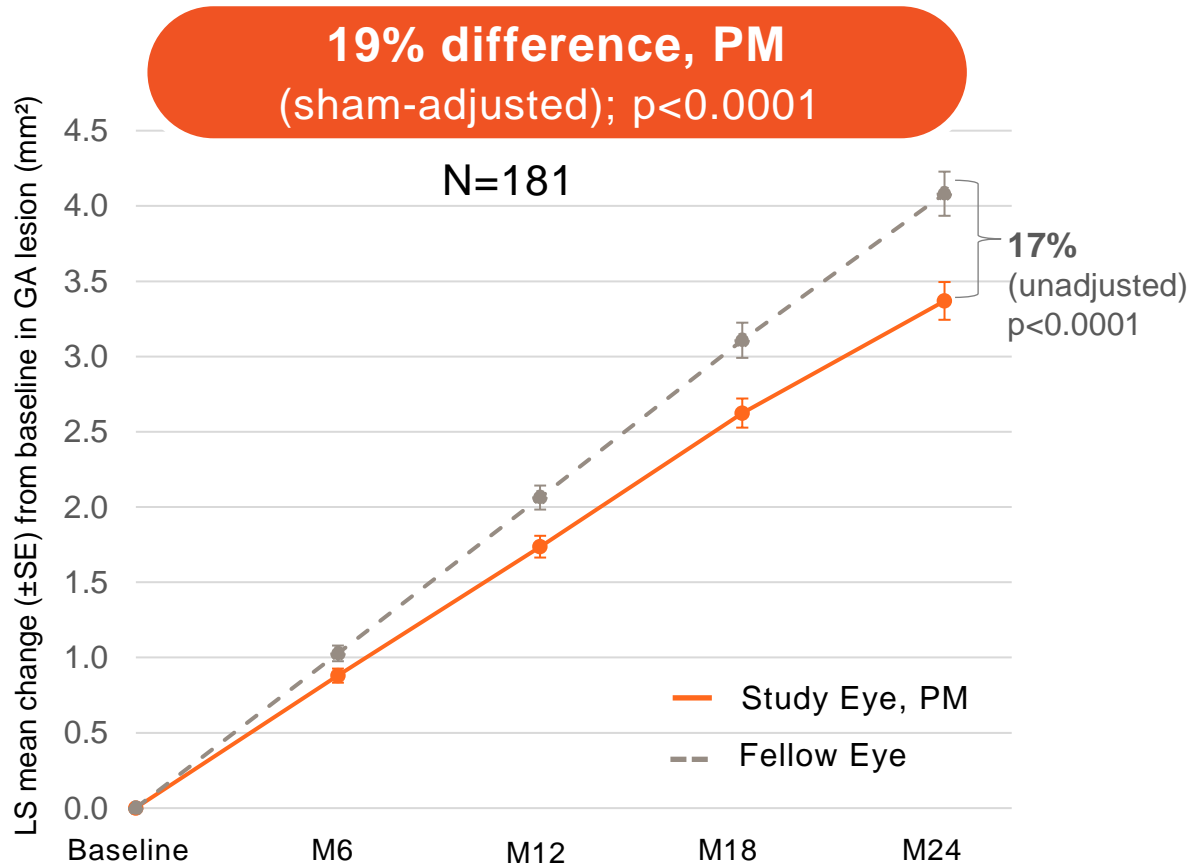
LS means estimated from MMRM analysis. The piecewise linear mixed-effects model evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 24, with knots at Months 6, 12 and 18 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope 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.

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Lesion growth in treated study eye vs untreated fellow eye

19% difference, PM
(sham-adjusted); p<0.0001

16% difference, PEOM
(sham-adjusted); p=0.0001

N=181

N=212

17% (unadjusted) p<0.0001

14% (unadjusted) p<0.0001

Study Eye, PM
Fellow Eye

Study Eye, PEOM
Fellow Eye

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

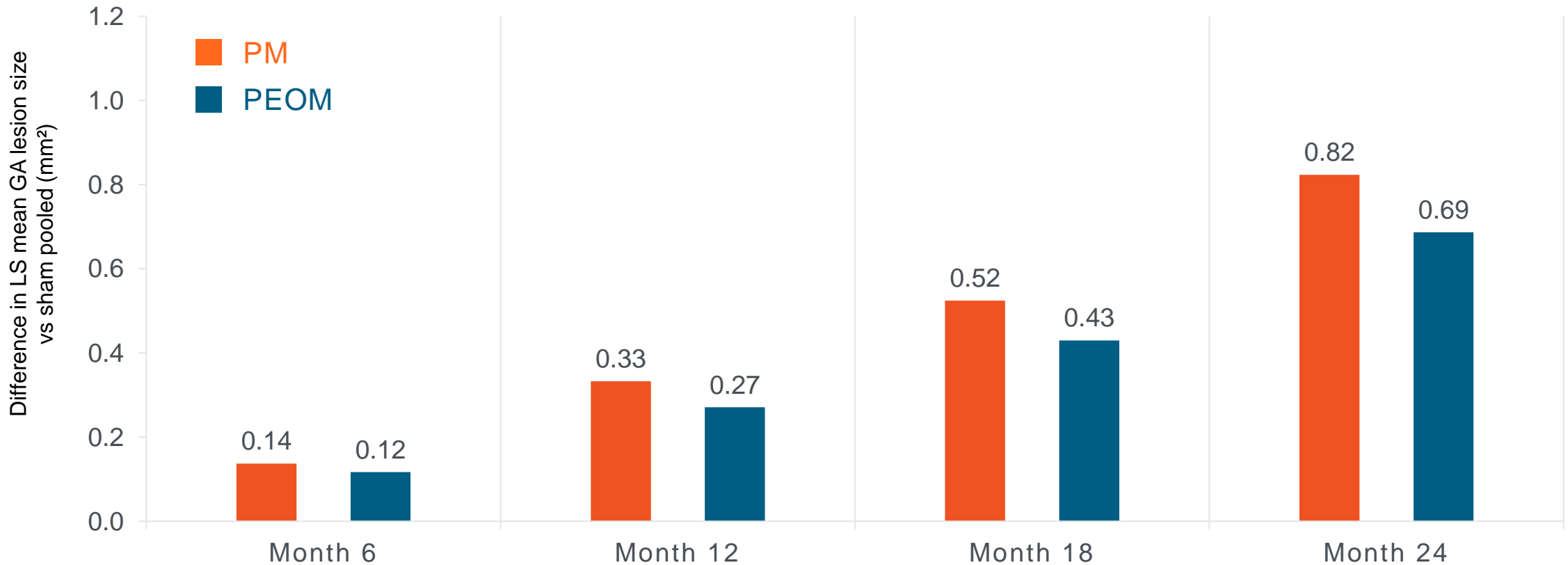Baseline M6 M12 M18 M24

(all p-values are nominal)

Sham study eye vs fellow eye: 2% faster growth (p=0.5573)

LS means estimated from a mixed-effects model for repeated measures. Data is presented for subjects with bilateral GA with fellow eyes that satisfied the following characteristics at baseline: absence of CNV in the medical history; baseline GA lesion size between 2.5 and 17.5 mm²; presence of any pattern of hyperautofluorescence in the junctional zone of GA; and GA not confluent with any peripapillary atrophy.
GA=geographic atrophy; LS=least squares; M=month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

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Cumulative preservation of retinal tissue

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.
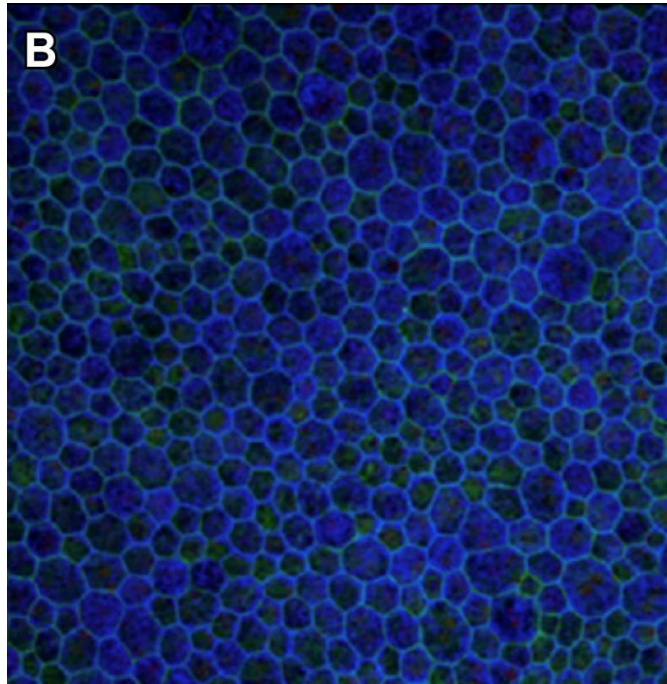
Example of GA lesion growth of 1.15 mm^2 on FAF
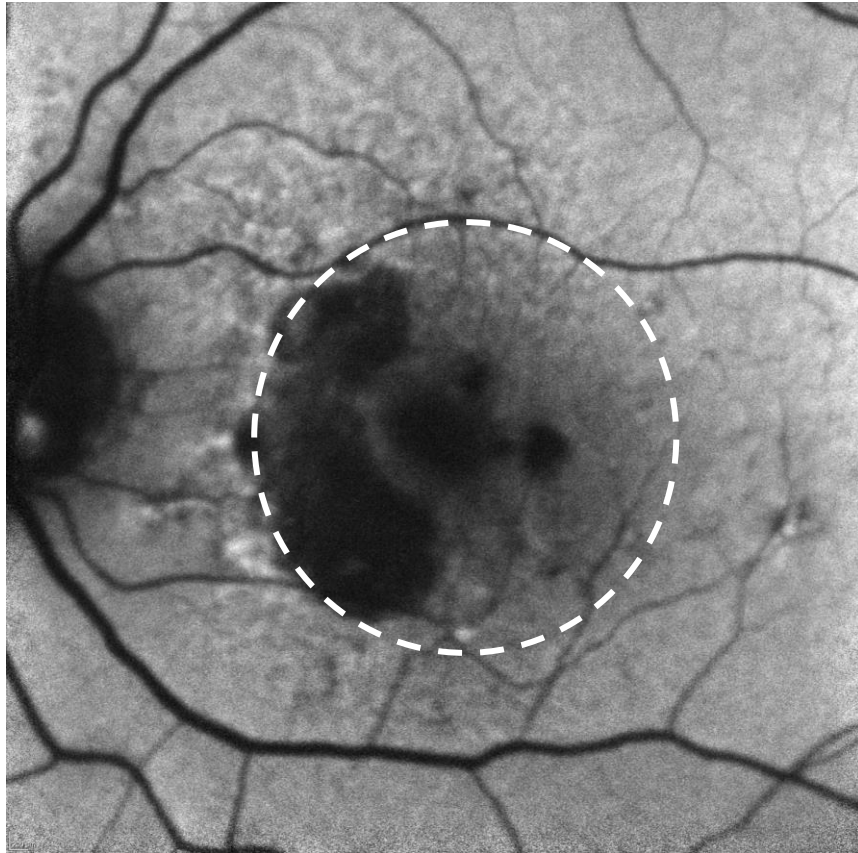
(Baseline)
4.581 mm^2
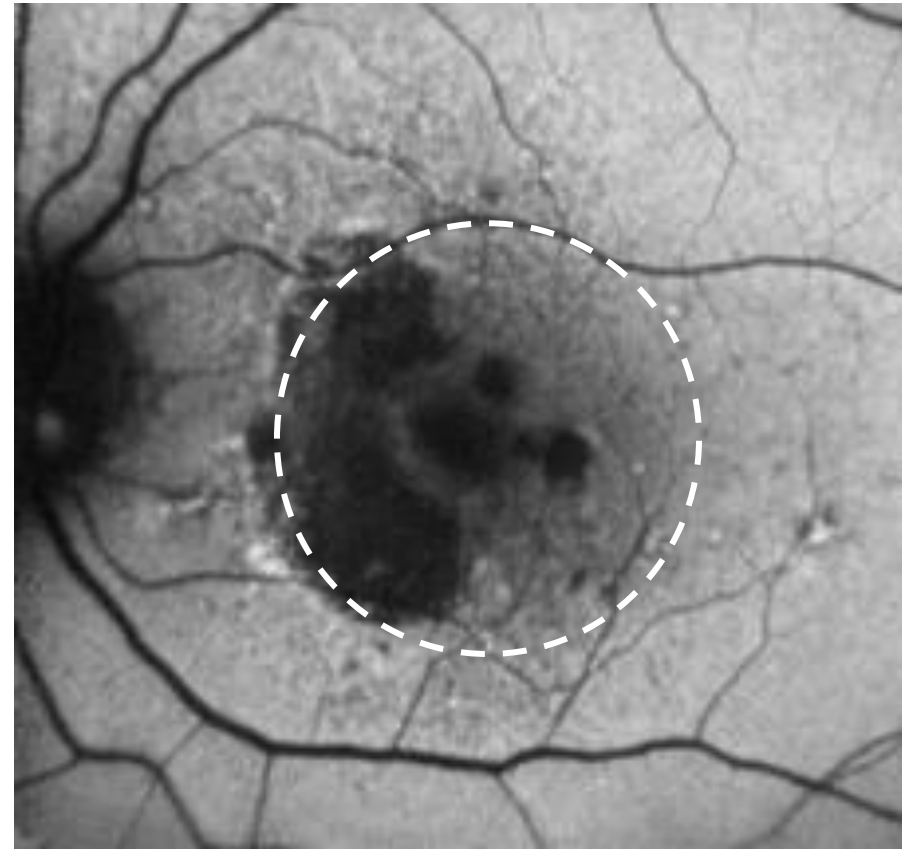
(Month 6)
5.726 mm^2

How does this translate into retinal cells saved?

Normal macular RPE density[1] ranges from 5082 to 7728 cells/mm^2

Represents 0.25mm x 0.25mm

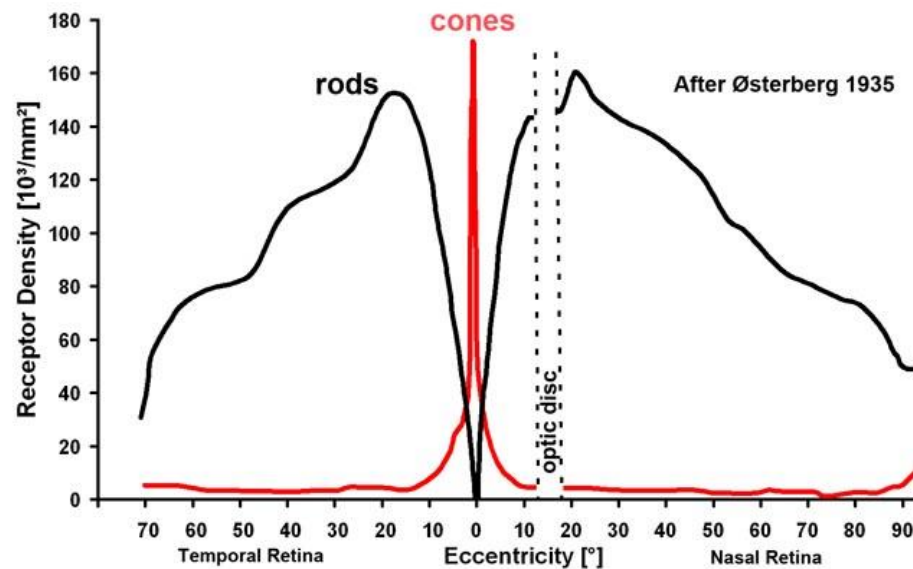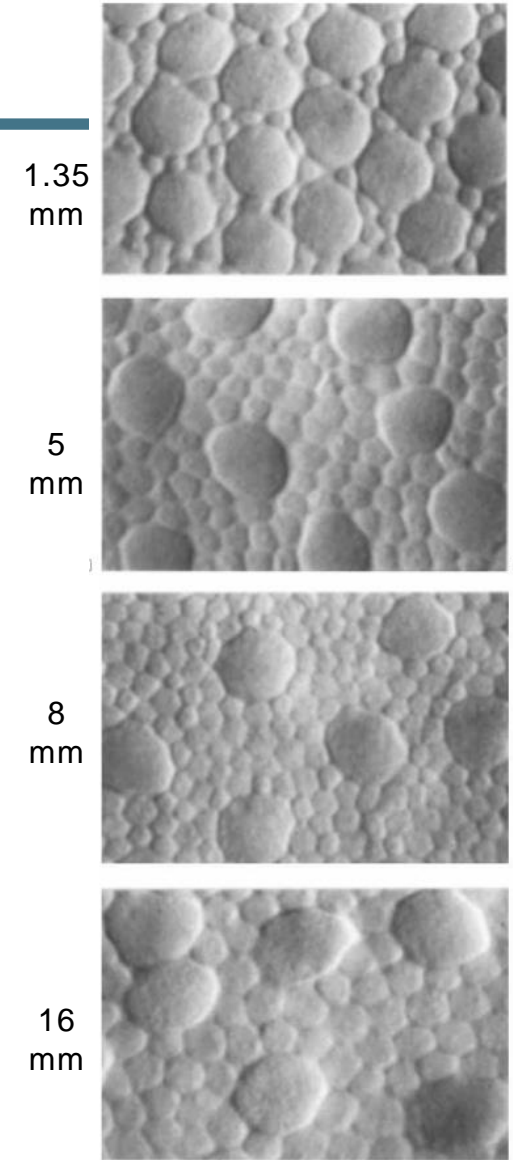Normal macular rod and cone PR density vary greatly depending on eccentricity from the fovea

Fig. 20. Graph to show rod and cone densities along the horizontal meridian.

1.35 mm

5 mm

8 mm

16 mm

Approx 0.04mm in width

Retina tissue and RPE preservation with pegcetacoplan monthly (estimated)

OAKS and DERBY combined

	PM (n=403)	PEOM (n=406)
Tissue saved	$0.82 \ mm^2$	$0.69 \ mm^2$
RPE cells saved	4200 – 6300	3500 – 5300

Based on macular RPE density[1] range
of 5082 cells/mm^2 to 7728 cells/mm^2

1 mm x 1 mm

4200 - 6300 RPE CELLS SAVED with Pegcetacoplan monthly
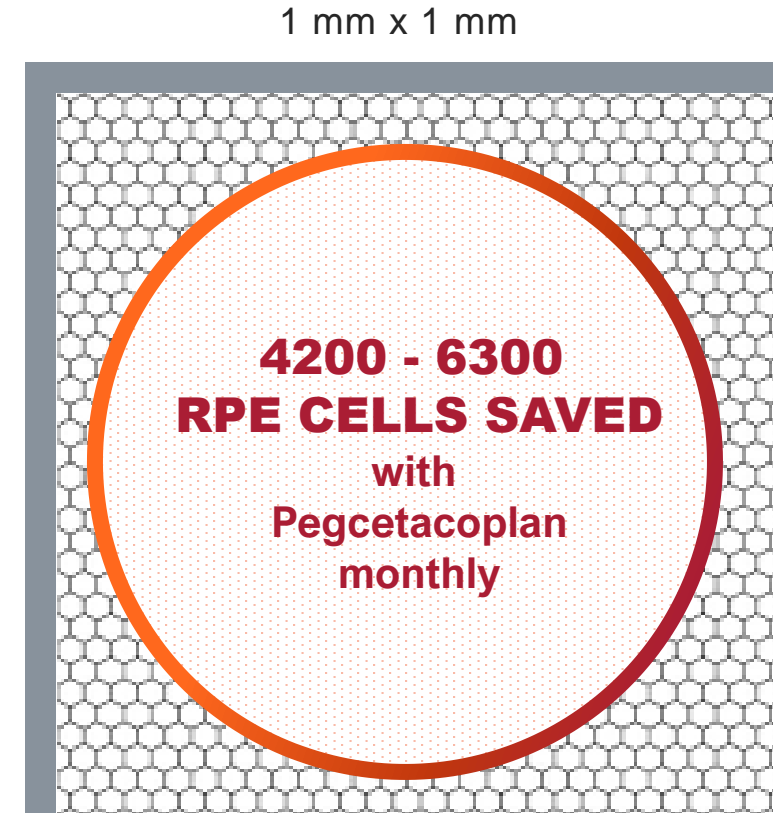
Retina tissue and RPE preservation with pegcetacoplan every other month (estimated)

OAKS and DERBY combined

	PM (n=403)	PEOM (n=406)
Tissue saved	0.82 mm^2	0.69 mm^2
RPE cells saved	4200 – 6300	3500 – 5300

Based on macular RPE density[1] range
of 5082 cells/mm^2 to 7728 cells/mm^2

1 mm x 1 mm

3500 – 5300 RPE CELLS SAVED with Pegcetacoplan EOM

PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; RPE=retinal pigment epithelium.
1. Ach T et al. *IOVS* 2014;55:4832–4841.

Nonsubfoveal subgroup: Reductions in GA lesion growth

all p-values are nominal

26%, PM
p<0.0001
22%, PEOM
p<0.0001

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

Baseline — M6 — M12 — M18 — M24

PM (n=158)   **PEOM** (n=155)   **Sham** (n=133, pooled)
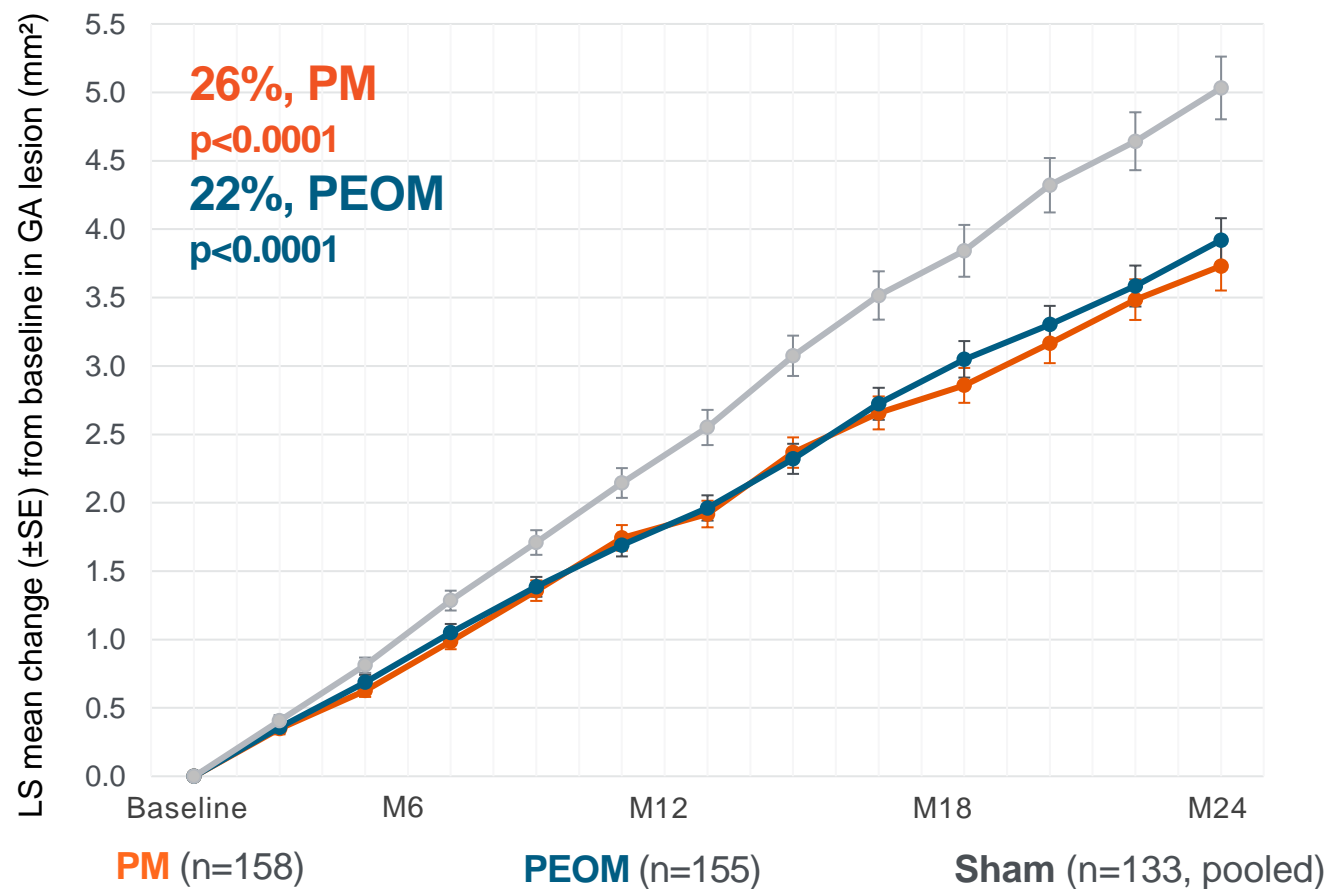
Nonsubfoveal synonymous with extrafoveal. LS means estimated from MMRM analysis. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the 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.

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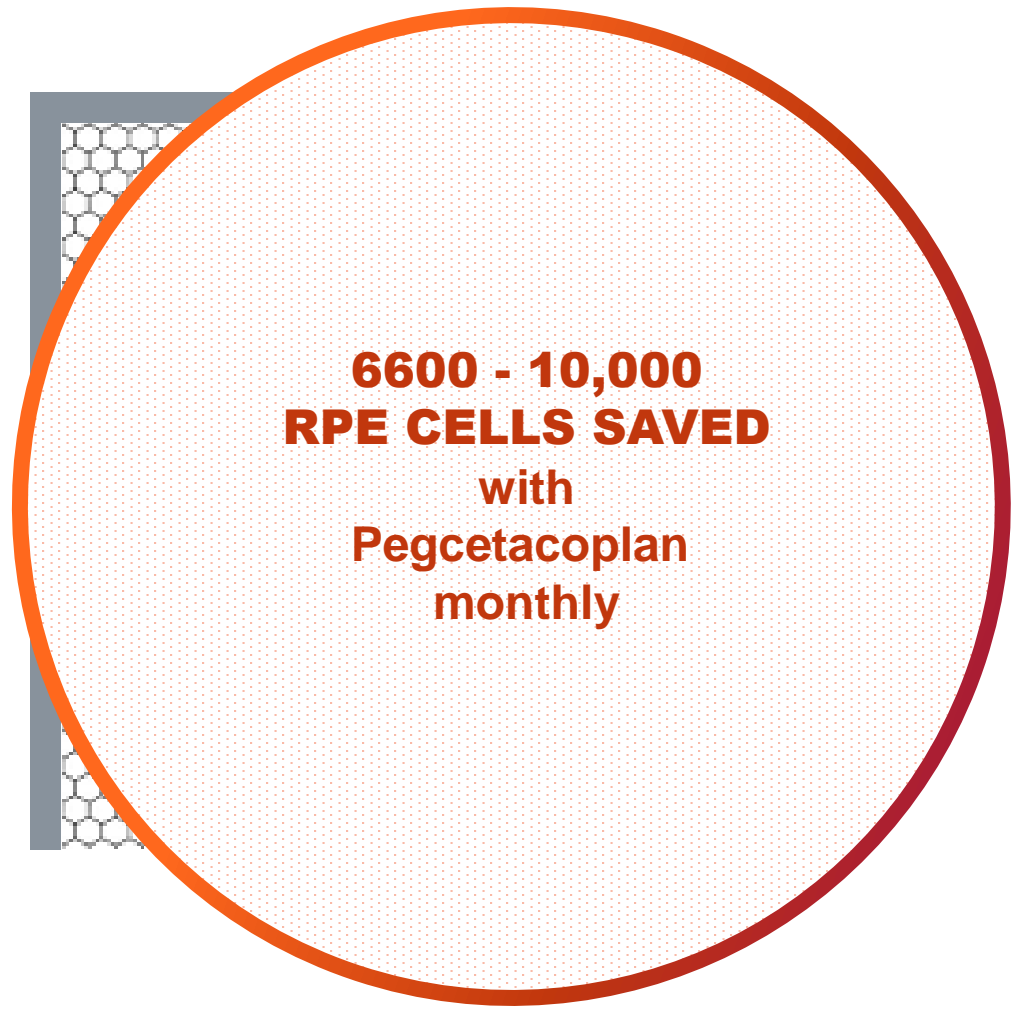# Cumulative preservation of retinal tissue in NSF lesions
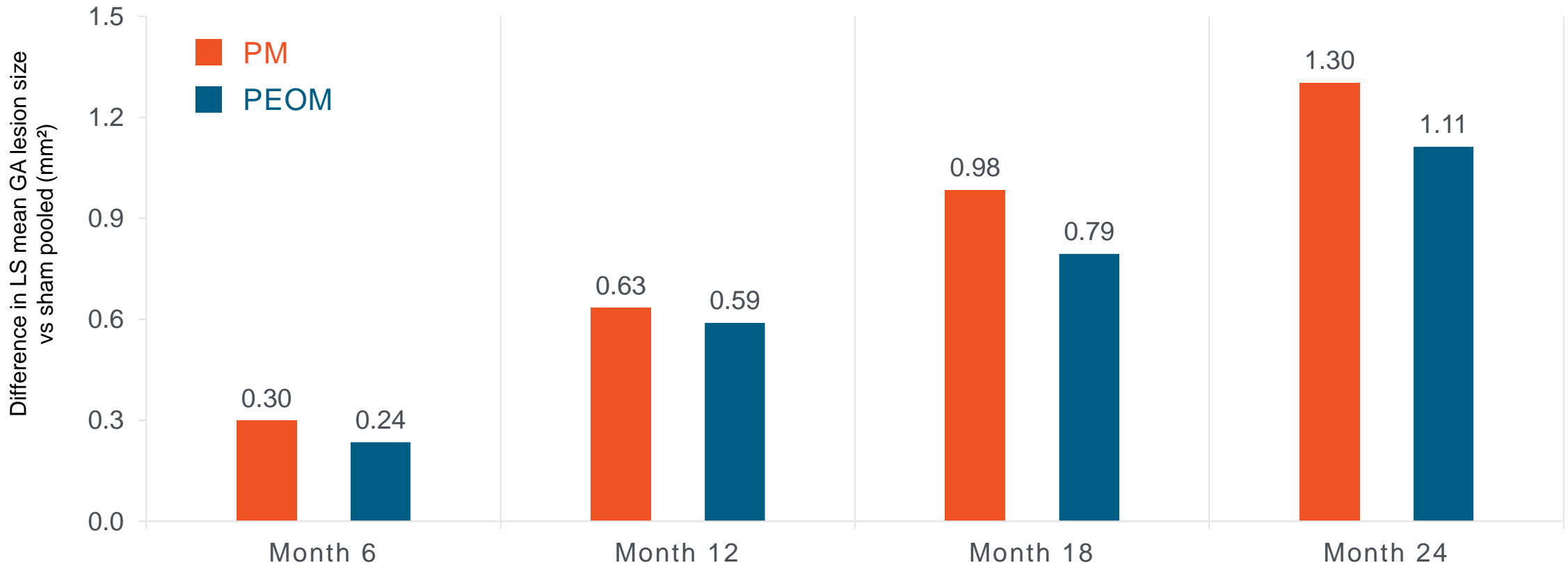
Absolute cumulative difference in lesion size vs pooled sham at Month 6, Month 12, Month 18, and Month 24 ('preserved area') from main MMRM analysis of mITT population. Fovea size calculated from average diameter of 1.5 mm per Kolb et al., *The Architecture of the Human Fovea.* GA=geographic atrophy;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

Retina tissue and RPE preservation in NSF lesions with pegcetacoplan monthly (estimated)

Subgroup analysis: Nonsubfoveal lesions

	PM (n=158)	PEOM (n=155)
Tissue saved	1.30 mm^2	1.11 mm^2
RPE cells saved	6600 – 10,000	5600 – 8600

Based on macular RPE density[1] range
of 5082 cells/mm^2 to 7728 cells/mm^2

6600 - 10,000 RPE CELLS SAVED with Pegcetacoplan monthly

Retina tissue and RPE preservation in NSF lesions with pegcetacoplan every other month (estimated)

Subgroup analysis: Nonsubfoveal lesions

	PM (n=158)	PEOM (n=155)
Tissue saved	1.30 mm^2	1.11 mm^2
RPE cells saved	6600 – 10,000	5600 – 8600

Based on macular RPE density[1] range
of 5082 cells/mm^2 to 7728 cells/mm^2

1 mm x 1 mm
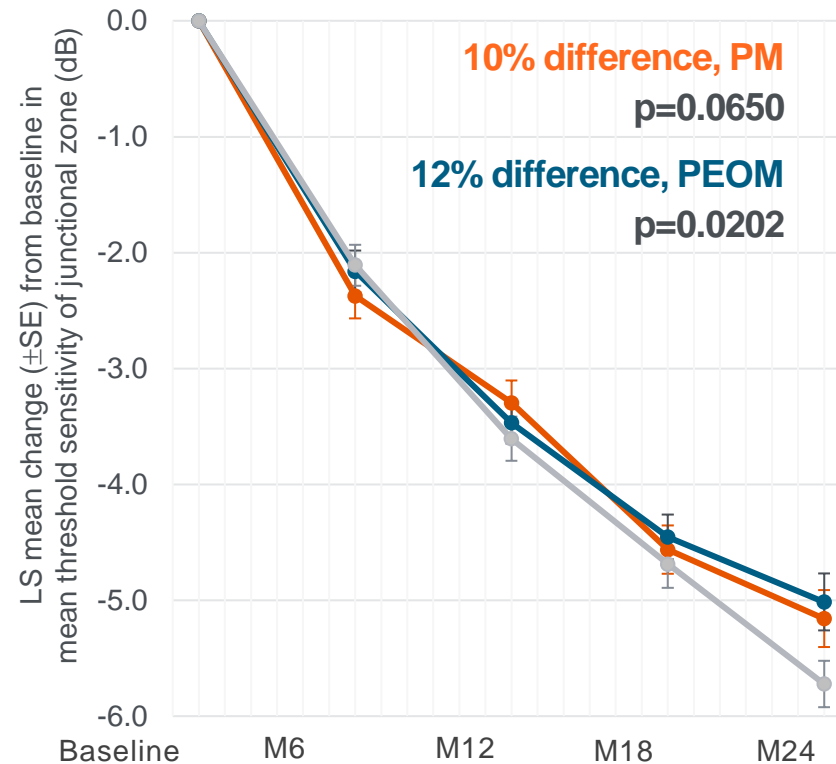
**5600-8600
RPE CELLS SAVED
with
Pegcetacoplan EOM**
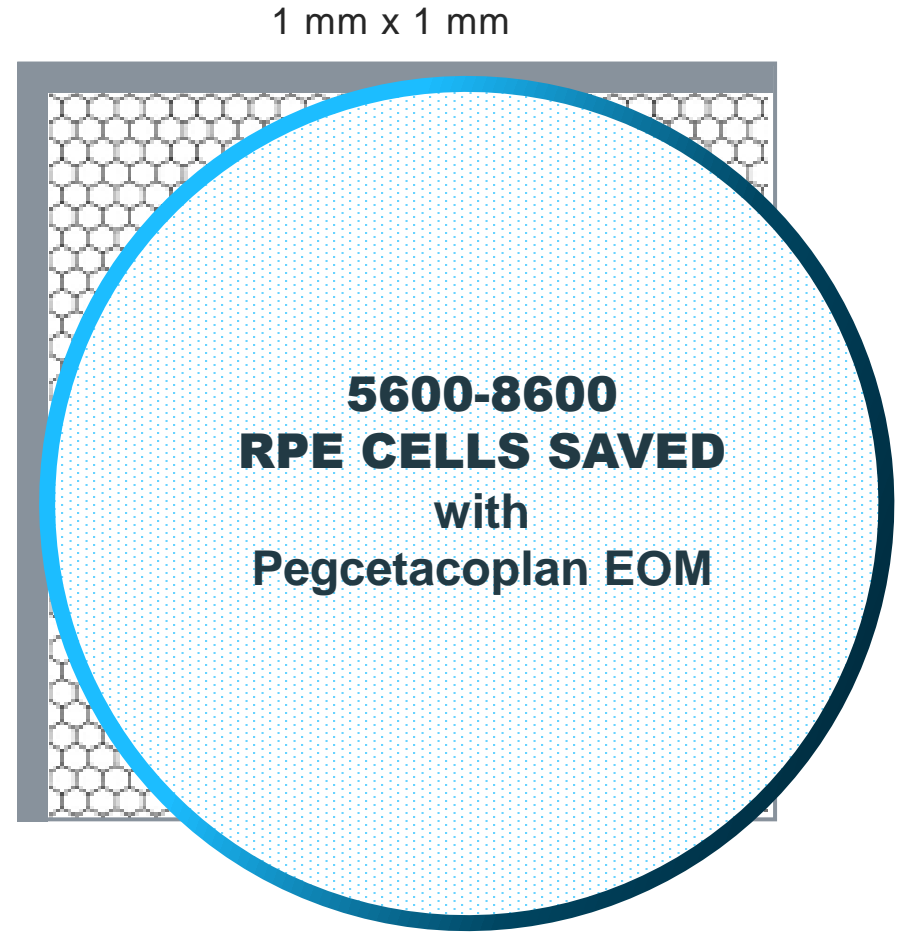
Pegcetacoplan effect on preserving retinal cells supported by signal of functional benefit on microperimetry
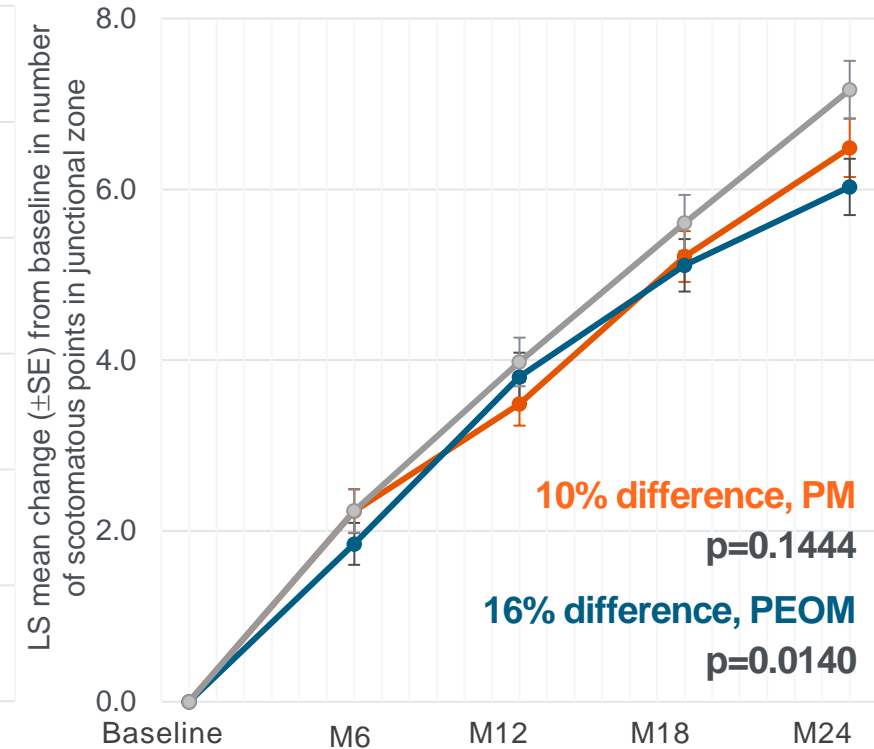

MP in the junctional zone (post-hoc)
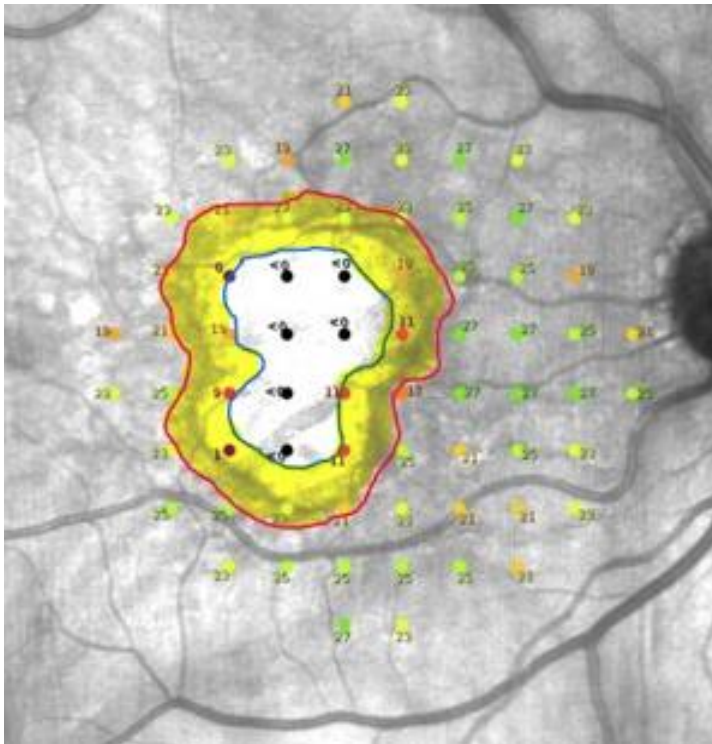
Mean threshold sensitivity (dB)

10% difference, PM
p=0.0650

12% difference, PEOM
p=0.0202

Number of scotomatous points

10% difference, PM
p=0.1444

16% difference, PEOM
p=0.0140

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. All p-values are nominal. dB=decibel; LS=least square; M=month; mITT=modified intent-to-treat; MP=microperimetry; MMRM=mixed-effects model for repeated measures; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Conclusions

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

- Pegcetacoplan slows GA progression
  - with both monthly and every other month dosing
  - in both nonsubfoveal and subfoveal lesions
  - with increasing effects over time

- Based on the area of retinal tissue preserved, between 3500–10,000 RPE are saved with 2 years of treatment, which corresponds with a much larger number of PR cells saved.

- Microperimetry findings in the junctional zone suggest functional benefit in the retinal tissue preserved with pegcetacoplan

GA=geographic atrophy; RPE=retinal pigment epithelium