Case Study:
GA Clinical Trials

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Financial Disclosures

- AAVantgarde Bio (C, S)
- Alcon (C)
- Abbvie (C)
- Alzheon (C)
- Alexion (C)
- Annexon Biosciences (C)
- AsclepiX (C)
- Aviceda (C)
- Bayer (C)
- Bausch and Lomb (C)
- Beacon Therapeutics/AGTC (C)
- Biogen Idec (C)
- Bionic Vision Technologies (C)
- Boehringer Ingelheim (C)
- Carl Zeiss Meditec (C, G)
- Complement Therapeutics (C)
- Duet Therapeutics (C)
- Exegenesis Bio (C)
- Galimedix (C)
- Genentech/Roche (C)
- Innovent (C)
- iRenix (C)
- Astellas (C)
- jCyte (C)
- Kanghong / Vanotech (C)
- Kera Therapeutics (C)
- Kodiak (C)
- Kriya Therapeutics (C)
- Nanoscope Therapeutics (C)
- Novartis (C)
- Ocular Therapeutix (E, S)
- Ocuphire (C)
- Oculis (C, S)
- Omeros (C)
- Palatin (C)
- Ray Therapeutics (C)
- RegenxBio (C)
- Retinal Sciences (C)
- ReVana (C)
- Roivant (C)
- Samsung Bioepsis (C)
- Sandoz / Coherus (C)
- Stealth Biotherapeutics (C)
- Stuart Biotherapeutics (C)
- Thea (C)
- Therini Bio (C)
- Tilak (C)
- Unity Biotechnology (C)
- VisgenX (C)

VA loss in GA

- BCVA declines at a rate of around 5 ETDRS letters/year
- BCVA correlates poorly with total GA area
- Decline rate varies widely lesion location, size, appearance
- “Floor effect” at BCVA 45 letters (Snellen 20/125) with GA expansion

Table 5. Change in Visual Acuity of Study Eye from Initial Visit to 2-year Follow-up Visit* [Number (%) of Eyes]

Decrease in Visual Acuity (number of lines)	GA Eyes (n = 40)	Drusen Eyes (n = 9)
Stable or improved by ≤1.5 lines	5 (12.5)	3 (33)
<1	2 (5.0)	3 (33)
≥1 and <2	5 (12.5)	0 (0)
≥2 and <3	8 (20.0)	2 (22)
≥3 and <4	6 (15.0)	1 (11)
≥4 and <5	2 (5.0)	0 (0)
≥5 and <6	2 (5.0)	0 (0)
≥6	10 (25.0)	0 (0)
Median decrease in visual acuity (number of lines)	3	0.6
Change in logMAR	0.30	0.06

GA = geographic atrophy.

* $P = 0.004$ (Wilcoxon’s rank-sum test).

Sunness JS et al. 1997; Chakravarthy et al. 2018, Heier et al. 2020; Lindner et al. 2017, Shen et al. 2021.

Functional Biomarkers

- ≥15 letter delta
  - Improvement
  - Prevention of loss

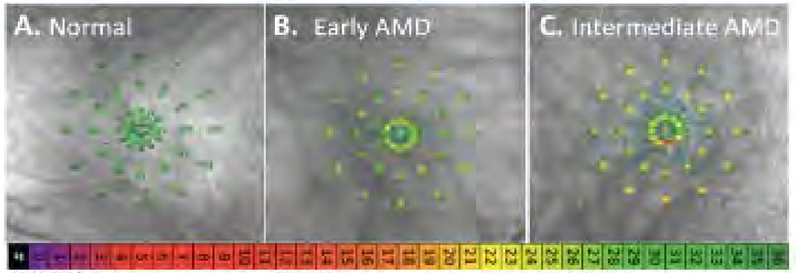
BCVA[1,2]

LLVA[3,4]

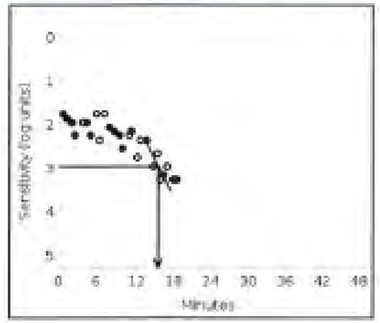
Color vision[3,5]

Contrast sensitivity[6,7]

Macular sensitivity[3,9,10]

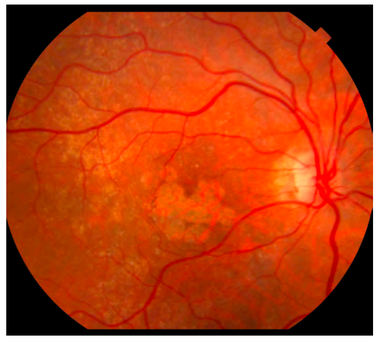
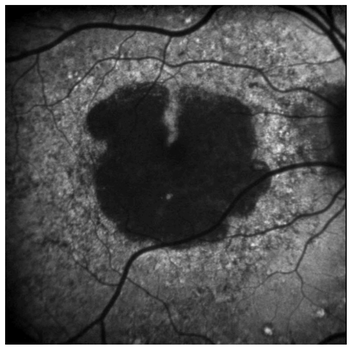
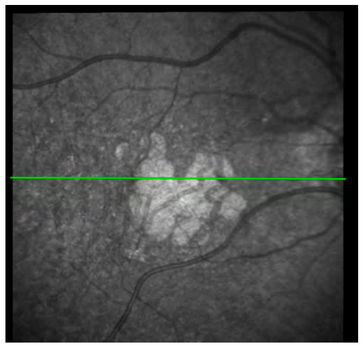
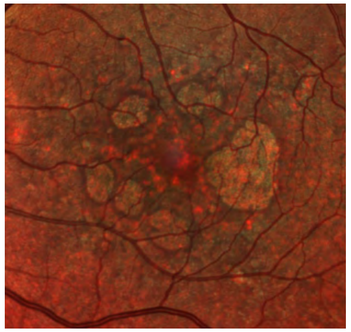
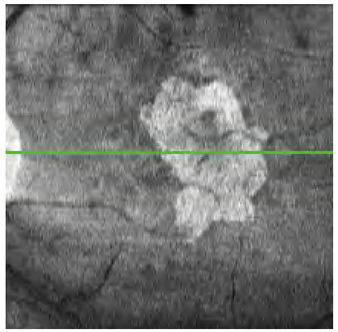


Dark adaptation[3,9,11]



No VA outcomes with central GA

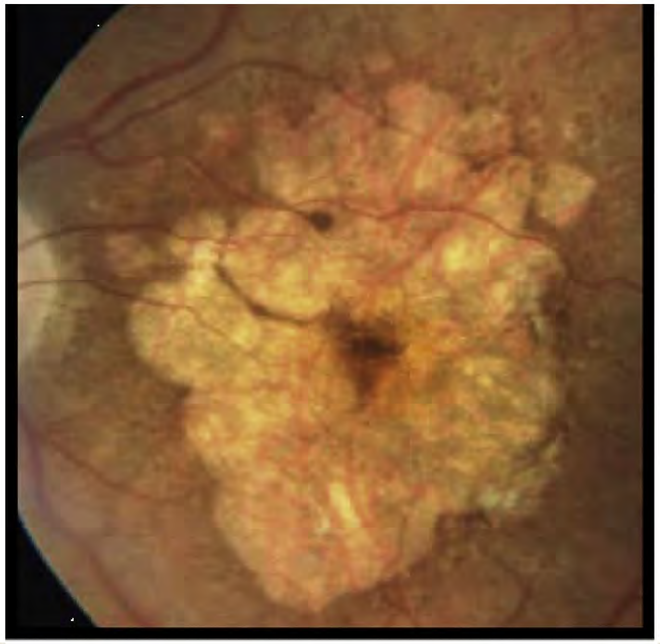
Modalities for Assessing atrophy

	Flash color	SW-FAF	NIR	Confocal/ Multicolor	OCT
					
Advantages	• Historical standard • Closest correlate to biomicroscopy • Visualizes broad range of fundus abnormalities • Best to image hemorrhages and pigmentary changes	• High contrast • Regulatory acceptance • Extensive experience • Already used for primary endpoint measurement • Strongly decreased signal correlates with loss of function • Allows for refined phenotyping and differential diagnosis	• Resistant to media opacities • Auxiliary for foveal assessment • Enables detection of reticular pseudodrusen and atrophy • Built-in in most OCT/SLO devices	• High precision and contrast • Displays many, but not all findings from CFP • Hyper-pigmentation difficult to distinguish from hemorrhage • Contrast between atrophy and fibrosis • Detection of pseudodrusen	• Broadly available • Cross-sectional morphology of retina, RPE and choroid • Correlated with histology • Validated to assess RPE atrophy progression and neovascular changes • Anatomical tracking functions for exact re-positioning of follow-up scans • Advances in lateral resolution and scanning speed expected in near future • Identification of pre-atrophic features • Comfortable for patients
Disadvantages	• Reduced contrast • Limited reliability • Strongly affected by optical media • Patient discomfort • Experienced examiner required	• Sensitive to nuclear lens opacities and vitreous floaters • Assessment of foveal region difficult • Semi-automated atrophy quantification may be hindered in certain conditions • Patient discomfort	• Lack of validation studies for late-stage AMD • Findings are of yet unstudied specificity • Cannot be used as stand-alone technology	• No true-color image • Mainly carrying the information from NIR • Limited evidence from validation studies • Limited availability	• Scan field limited • Interpretation strongly dependent on imaging quality • Lack of industry standards • 3D datasets require sophisticated analysis software and longer reading times for detailed slab analyses of retinal and choroidal layers • Automated segmentation imperfect and instrument dependent • Definition of atrophy border and relevance of certain prognostic biomarkers still controversial

Courtesy of Dr. Vas Sadda; AMD: age-related macular degeneration; CFP: colour fundus photography; NIR: near-infrared spectroscopy; OCT: optical coherence tomography; RPE: retinal pigment epithelium; SW-FAF: short-wavelength fundus autofluoresence. 1. Imaging Protocols in Clinical Studies in Advanced Age-Related Macular Degeneration: Recommendations from Classification of Atrophy Consensus Meetings, Ophthalmology, 2017

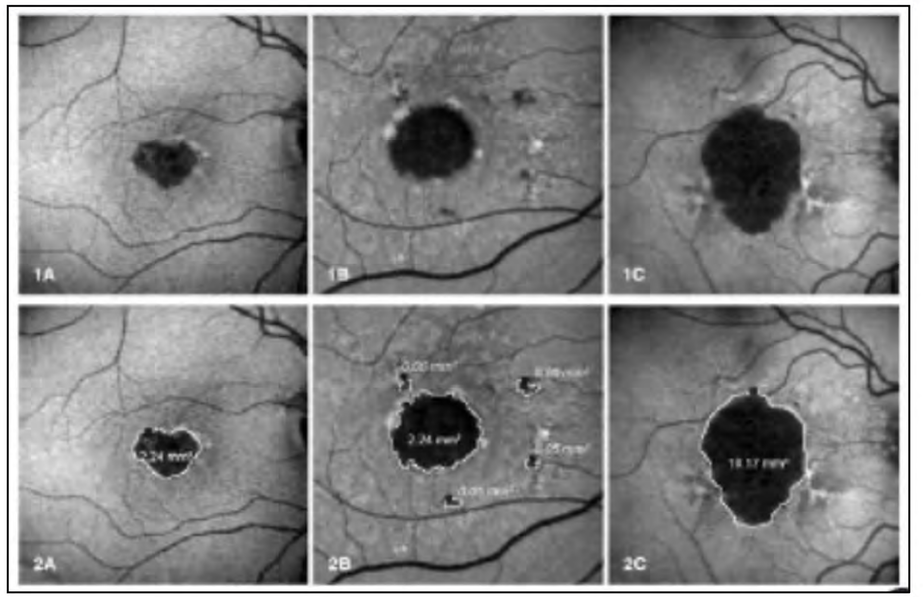
Imaging studies identify the clinical features of GA

A. Fundus photograph of geographic atrophy



Adapted from reference 1

B. Detection and quantification of atrophy on FAF



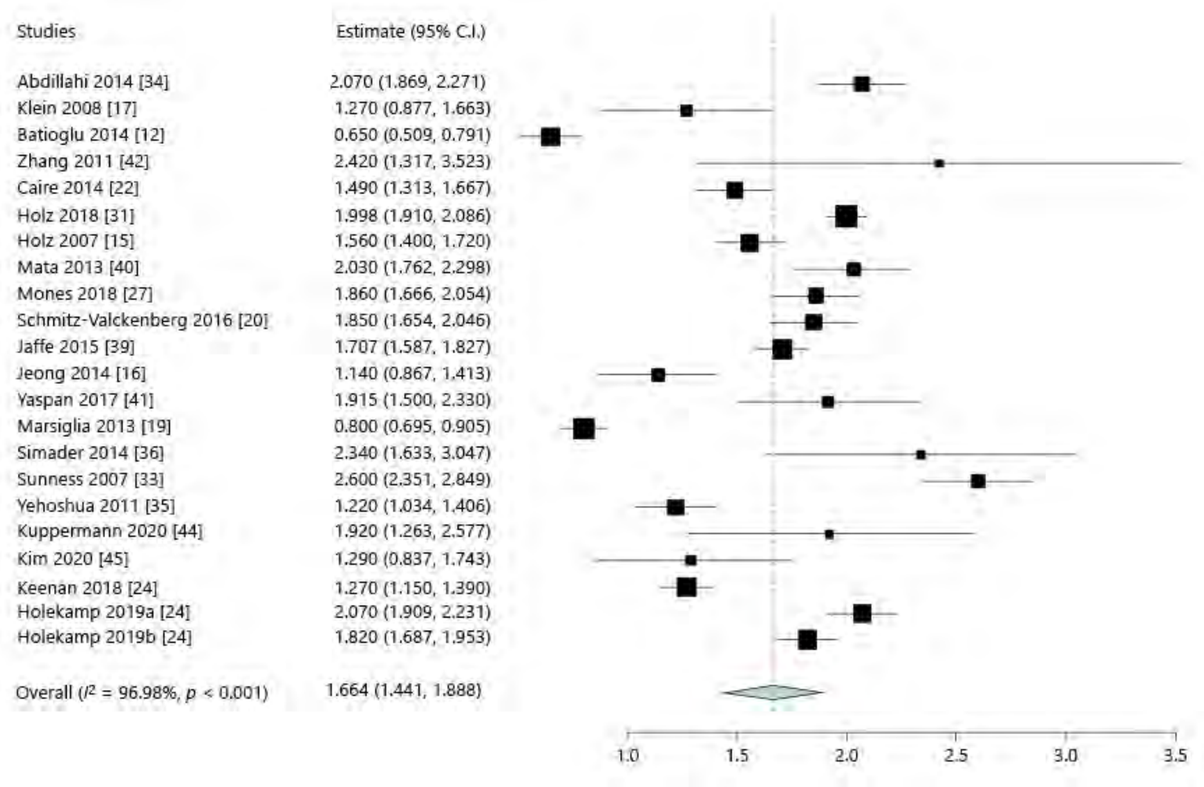
Adapted from reference 2

ETDRS=Early Treatment Diabetic Retinopathy Study; FAF=fundus autofluorescence; GA=geographic atrophy.

1. Fleckenstein M, et al. *Ophthalmology* 2018;125:369-390.
2. Danis RP, et al. Invest *Ophthalmol Vis Sci*. 2013;54:4548-54

Kinetics of GA progression are highly variable

- There is a substantial heterogeneity of GA growth rate across studies
- Across 23 studies, the pooled overall mean GA growth rate was **1.66 mm²/year**
- The mean GA growth rate ranged from **0.65 to 2.60 mm²/year** during the length of follow-up, ranging from 1 to 5 years



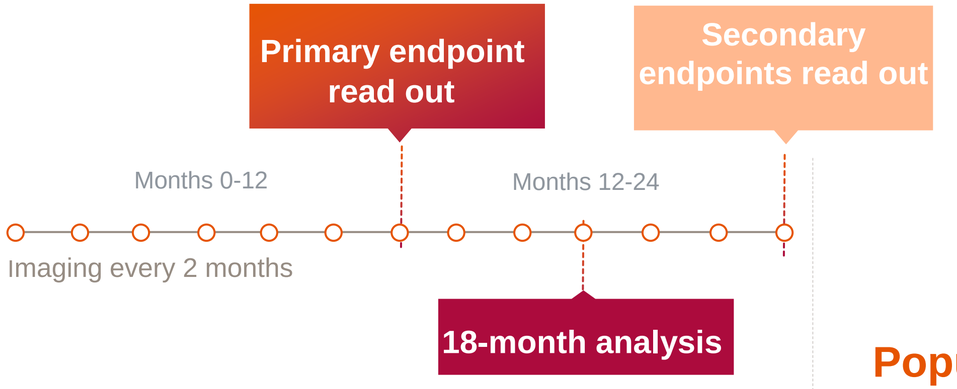
Forest tree plot for GA growth rate (mm²/year)
23 studies of 3,471 eyes from 3,078 patients

Wang J, et al. *Ophthalmic Res*. 2021;64(2):205-215.

Studies of Complement Inhibition

DERBY and OAKS: Two Phase 3 studies of intravitreal pegcetacoplan in patients with GA

Double masked



ELIGIBLE PATIENTS WITH GA

1,258 subjects from ~200 multinational sites

→ **PEGCETACOPLAN**
monthly (n~200 per study)
15 mg/0.1 mL

→ **PEGCETACOPLAN**
every other month (n~200 per study)
15 mg/0.1 mL

→ **SHAM**
monthly and every other month pooled (n~200 per study)

Population: patients with GA secondary to AMD (baseline characteristics well balanced)

Primary endpoint: change in total area of GA lesion(s) based on fundus autofluorescence (FAF) at month 12

Design: double masked, randomized

Duration: 2 years

Functional endpoints will be formally tested at 24 months

NCT03525600, NCT03525613

Determining Lesion Size: Region Finder

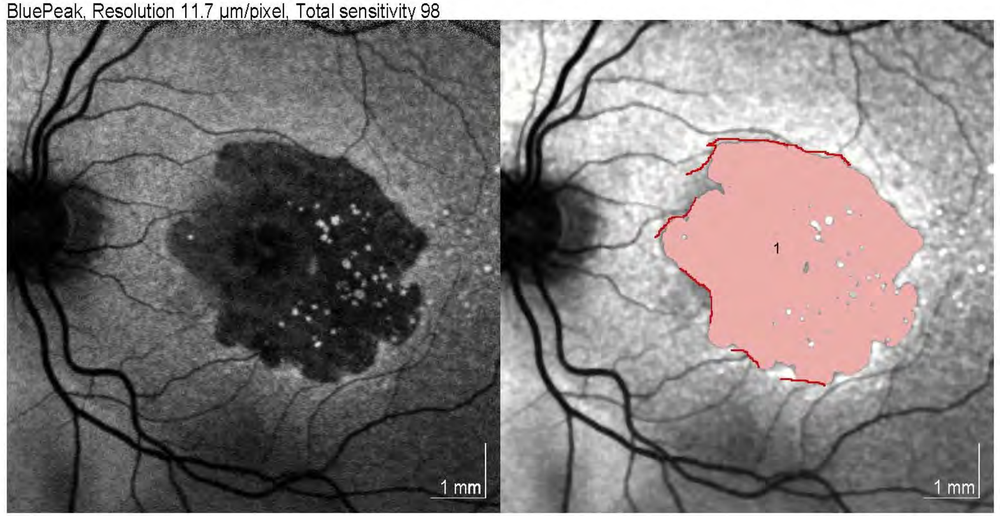
SPECTRALIS® RegionFinder™
Customized Report

HEIDELBERG ENGINEERING

Patient:	NOVARTIS LFG316A2102, 3004	**DOB:**	1/1/2001	**Gender:**	M
Patient ID:	---	**Exam.:**	5/25/2011		
Diagnosis:		**Comment:**			

OS

BluePeak, Resolution 11.7 µm/pixel, Total sensitivity 98



Reading Details

Date:	10/13/2011	Number of regions:	1
Time:	14:56:27	Perilesional pattern:	unseeded
Total region size:	13.487 mm²	Reader Name:	OCT

N°	Border Color	Size [mm²]	Growth Power [%]	Growth Limit [%]	min-max vessel [µm]	Strap Ratio
1		13.487	60	100	30 - 30	0.00

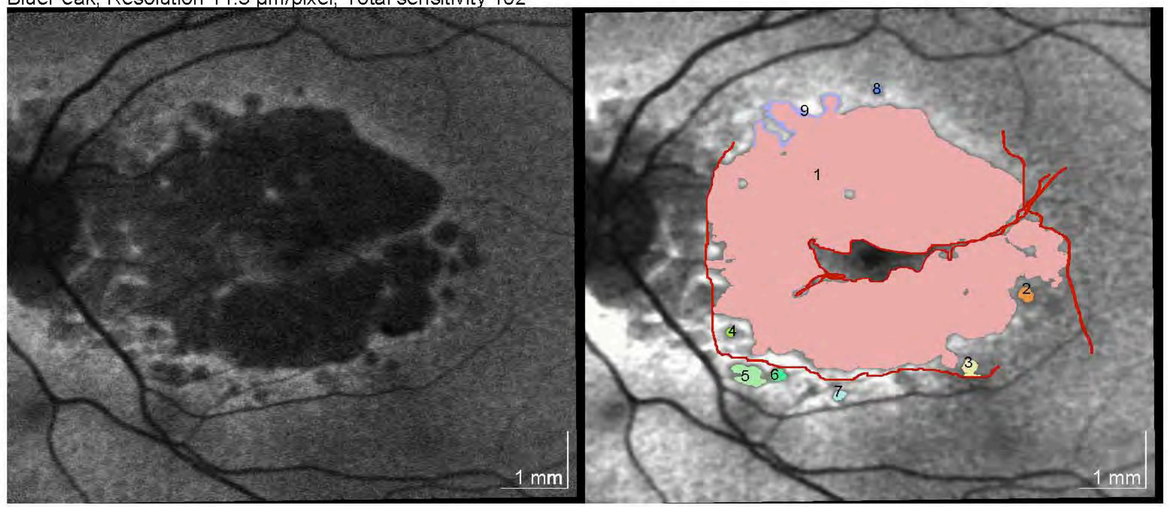
SPECTRALIS® RegionFinder™
Customized Report

HEIDELBERG ENGINEERING

Patient:	OPH2001, 308-025	**DOB:**	1/1/2001	**Gender:**	F
Patient ID:	308-S005	**Exam.:**	1/13/2011		
Diagnosis:		**Comment:**			

OS

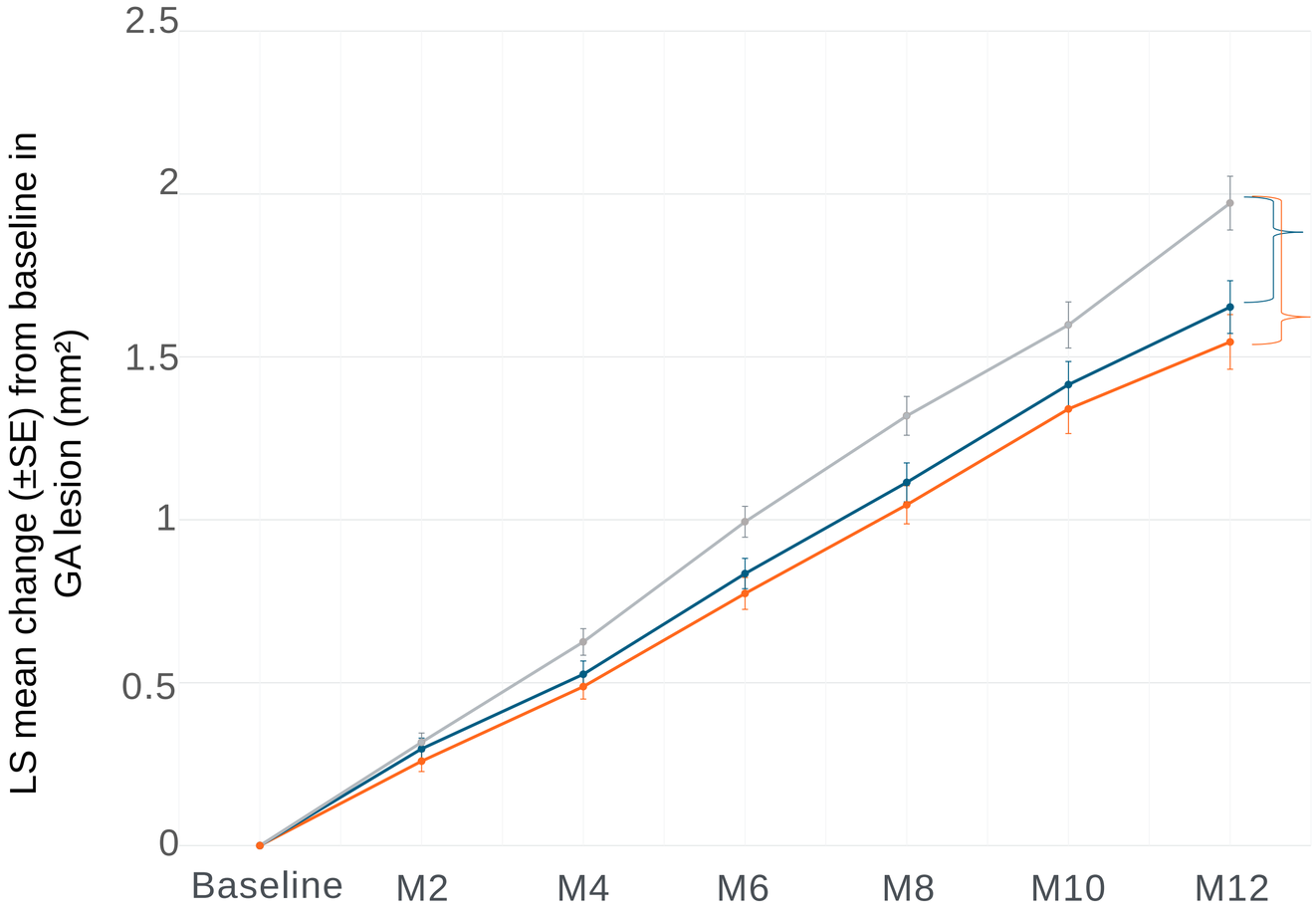
BluePeak, Resolution 11.3 µm/pixel, Total sensitivity 102



Reading Details

Date:	3/10/2011	Number of regions:	9
Time:	17:38:20	Perilesional pattern:	unseeded
Total region size:	16.877 mm²	Reader Name:	jaffe001

Pegcetacoplan met the primary endpoint in OAKS



16% (every other month) reduction
p=0.0052 vs sham

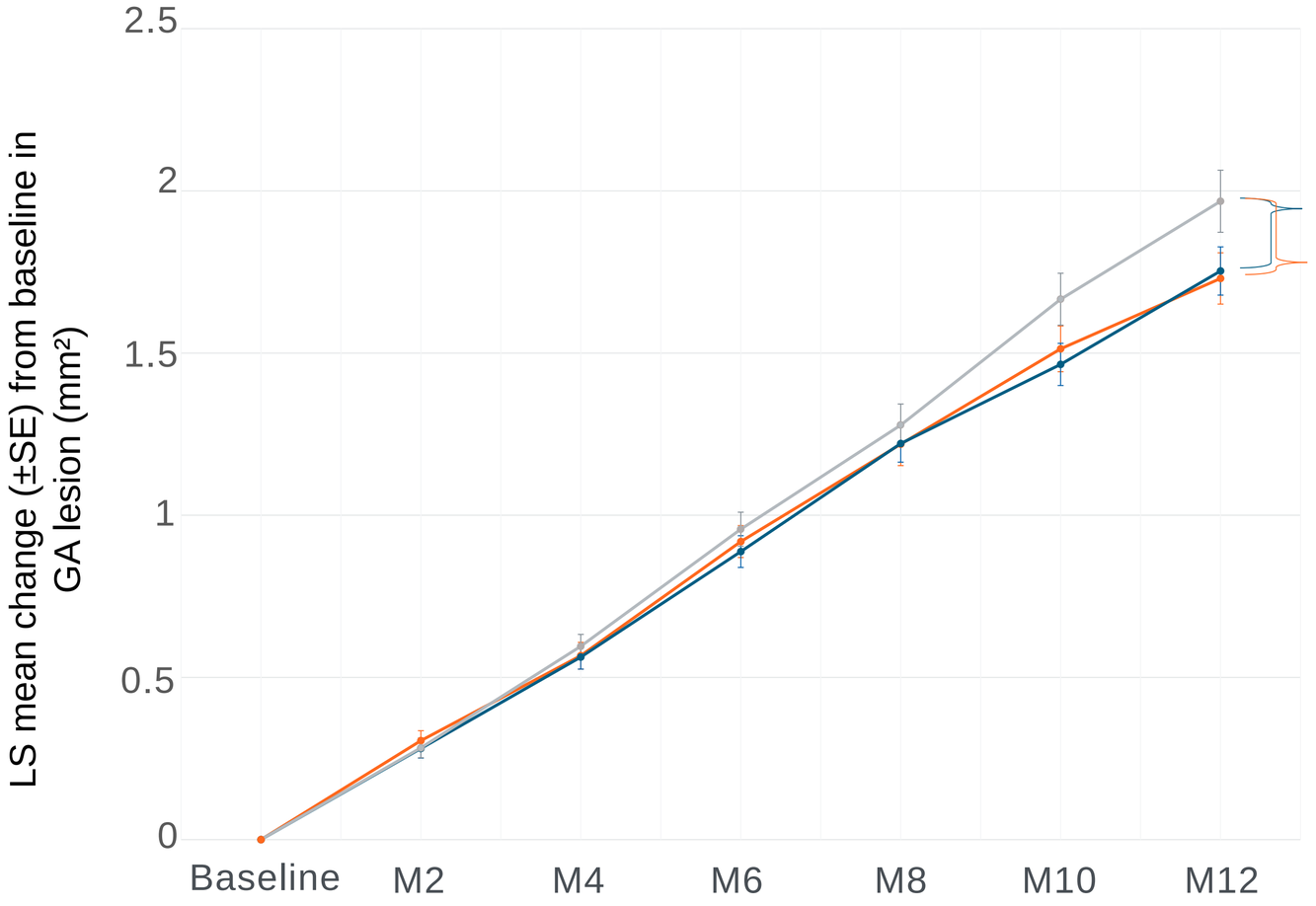
22% (monthly) reduction
p=0.0003 vs sham

Sham (n=206, pooled)

PEOM (n=205)

PM (n=202)

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

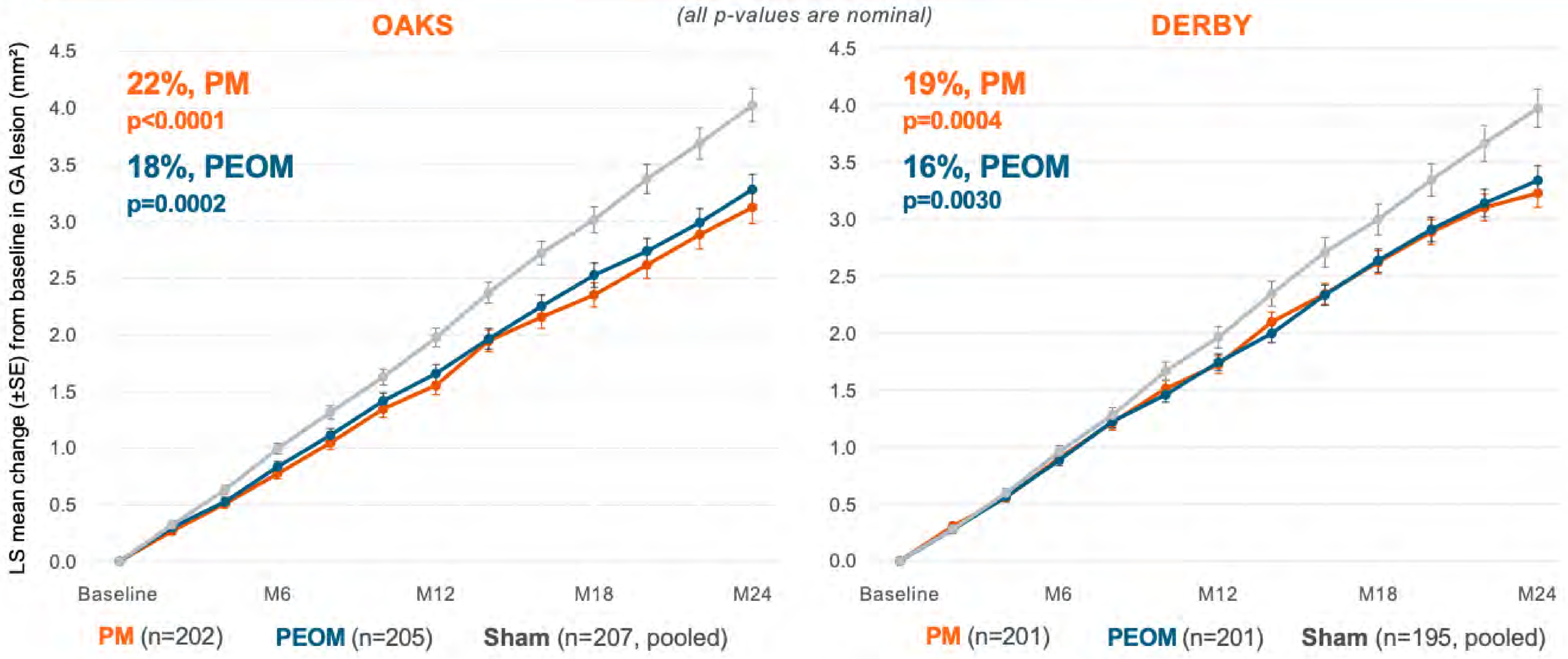
Sham (n=194, pooled)

PEOM (n=200)

PM (n=201)

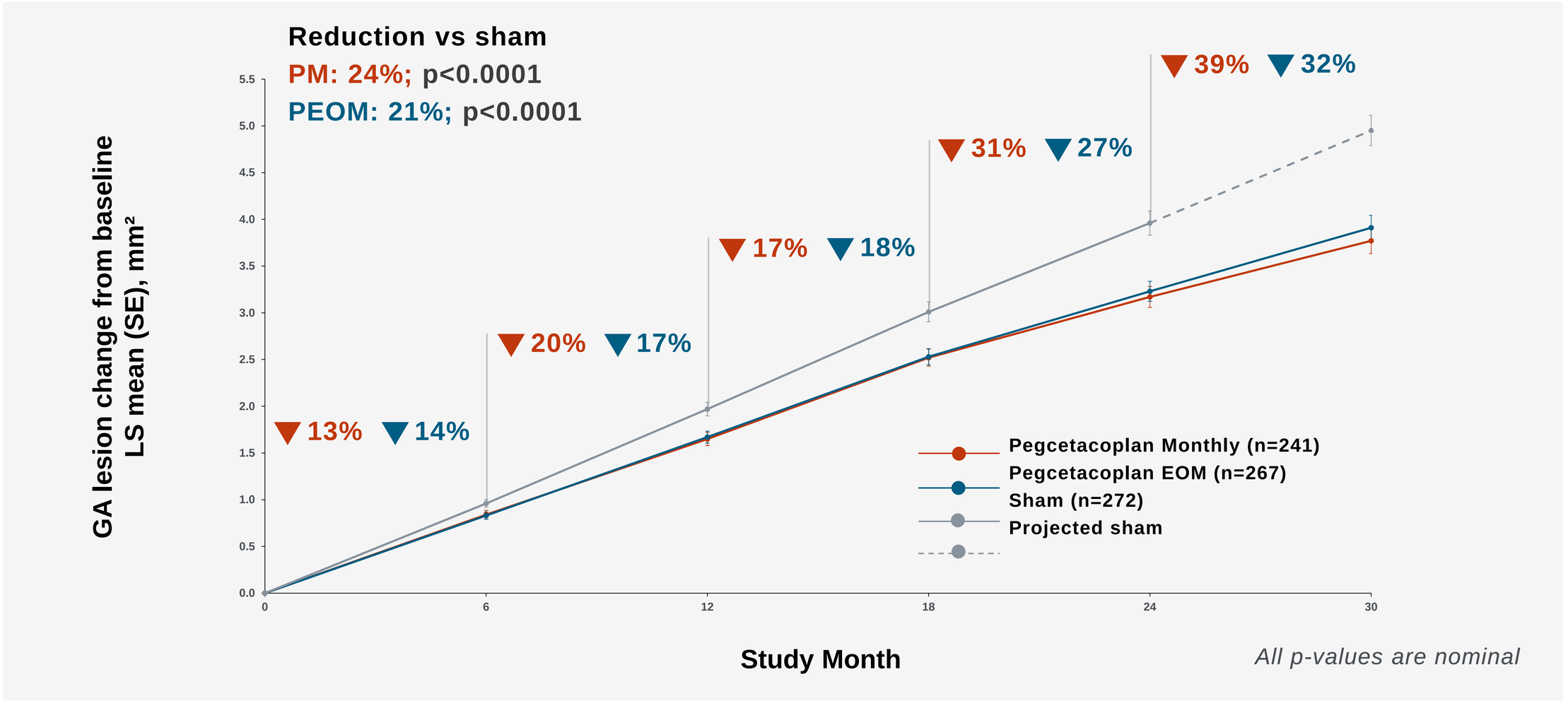
Reductions in GA lesion growth at Month 24

(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.

GALE: Reductions in GA Lesion Growth Following 30 Months of Continuous Treatment With Pegcetacoplan Increased Over Time

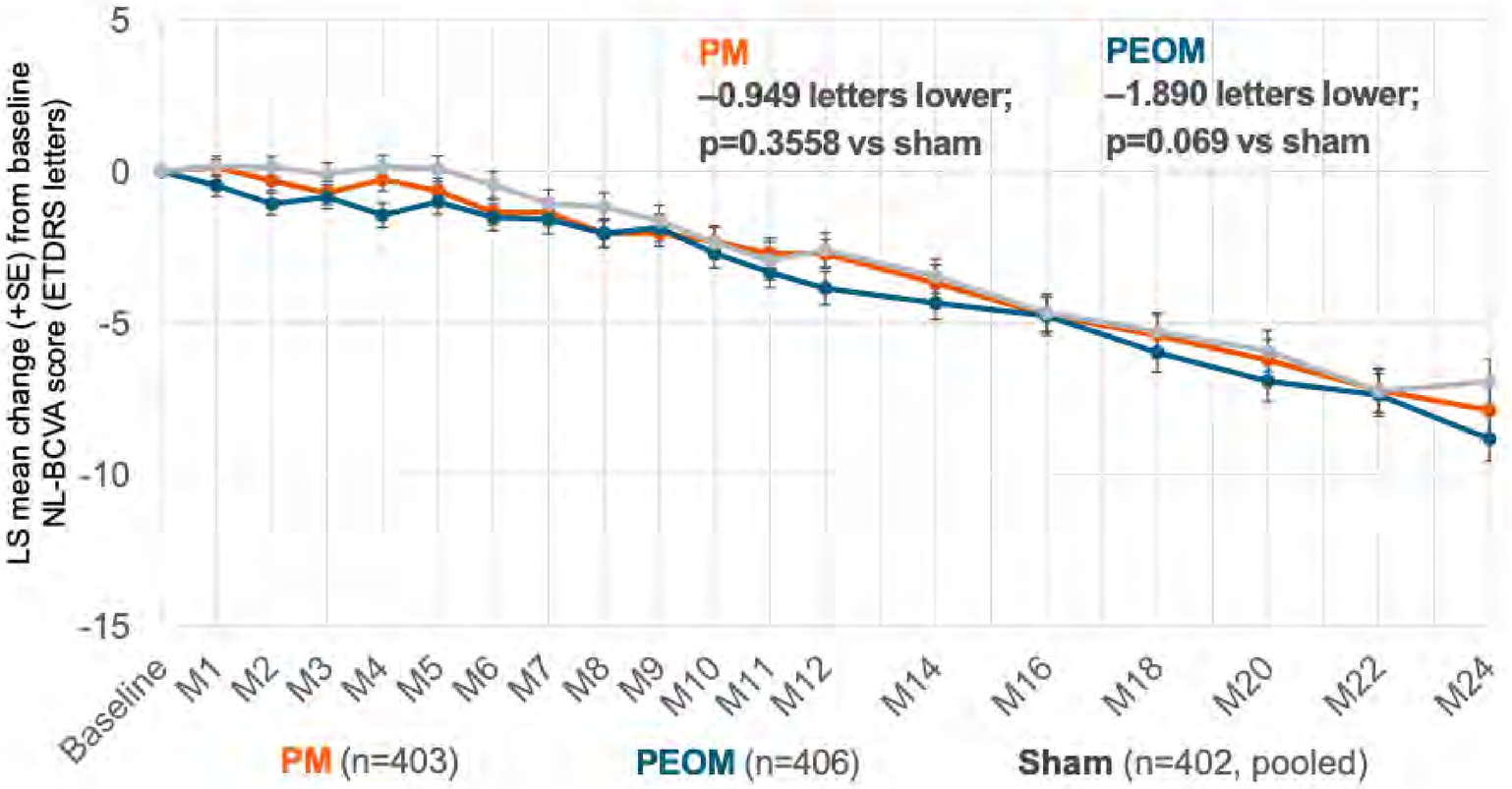


LS means estimated from a piecewise linear mixed-effects model that evaluated mean rate of change in GA area between pegcetacoplan arms and sham arm from baseline to Month 30, with knots at Months 6, 12, 18, and 24 allowing for the slope to be linear over each of the 6-month segments but to differ between segments (piecewise slope analysis). Mean rate of change of projected sham from Month 24 to Month 30 was estimated from the mean rate of change in each 6-month period from Month 0 to Month 24. The modified full analysis set was used for the analysis, defined as patients who are in OAKS/DERBY antecedent study's ITT set, have not been enrolled in APL2-103, and received ≥1 injection of pegcetacoplan in GALE. Projected sham is shown with a dashed line. Data shown for patients who continued into the GALE trial after OAKS and DERBY.

EOM, every other month; **GA,** geographic atrophy; **ITT,** intent to treat; **LS,** least-squares; **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.

Post hoc analysis: Methods and quartile definitions

OAKS DERBY 24 Months

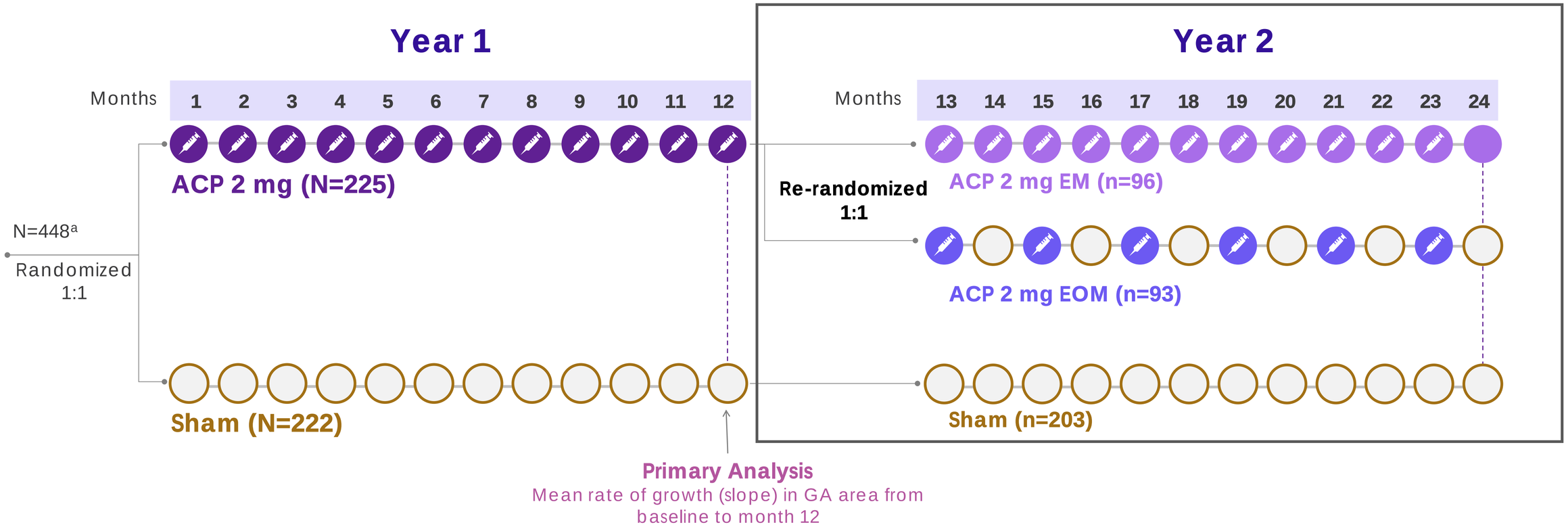
GA progression measured by change in lesion area (mm^2) from baseline to Month 24

- GA progression **by quartiles of growth** assessed in the overall patient population
- Patients needed to have a Month 24 lesion growth measurement to be included in the analysis
- Total n=1000; 250 per quartile

Lesion growth quartiles	Growth over 2 years (mm^2)
Quartile 1 slowest progressors	**≤2.08**
Quartile 2	**>2.08–≤3.13**
Quartile 3	**>3.13–≤4.53**
Quartile 4 fastest progressors	**>4.53**

GA=geographic atrophy.

GATHER2 is a 2-year, phase 3, international, multicenter, prospective, randomized, double-masked, sham-controlled study (NCT04435366)



Year 2 Objectives

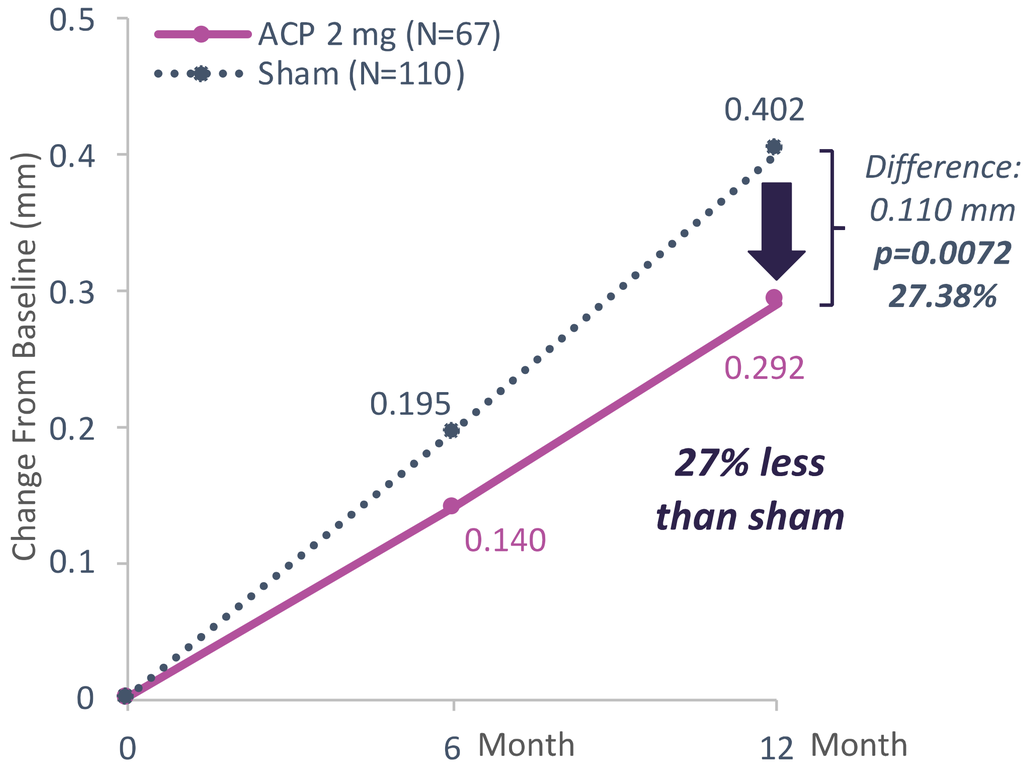
Evaluate efficacy and safety of re-randomized population of ACP monthly (EM) and every other month (EOM) through year 2

Note: The 24-month objective used observed data.
[a]448 randomized, with 447 treated (1 patient in sham did not receive treatment after randomization).
ACP, avacincaptad pegol; GA, geographic atrophy.
Khanani AM, et al. *Lancet*. 2023;402(10411):1449-1458.

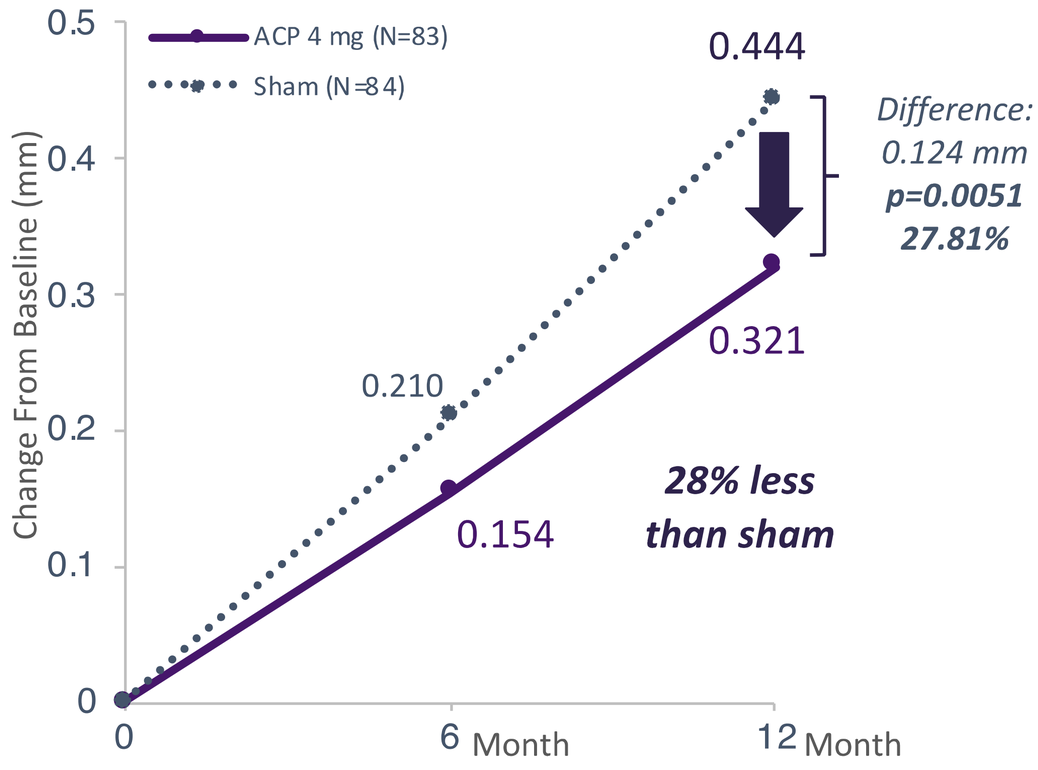
GATHER1: Primary outcome endpoint ACP vs sham

MEAN CHANGE FROM BASELINE IN SQUARE-ROOT GA LESION AREA OVER 12 MONTHS

ACP 2 mg vs sham*

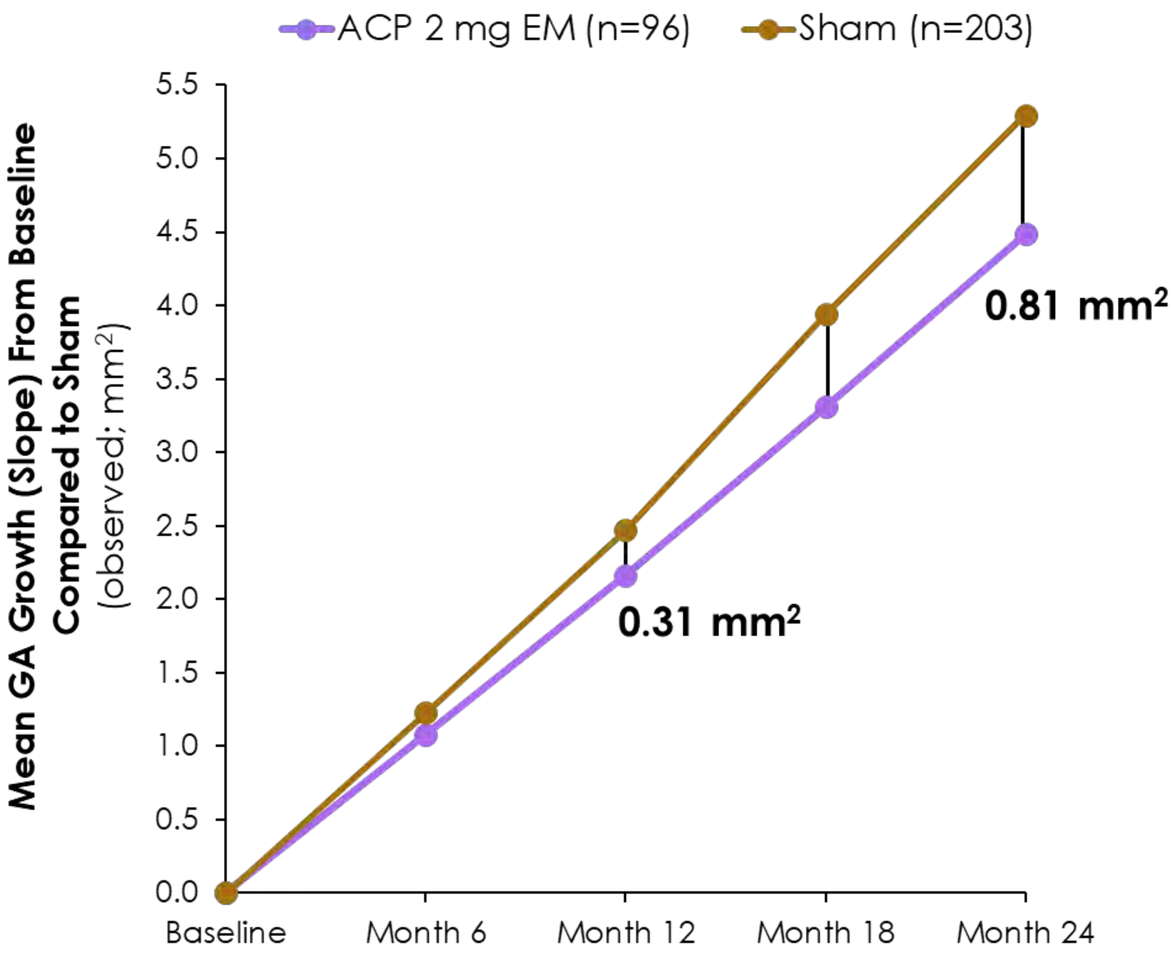


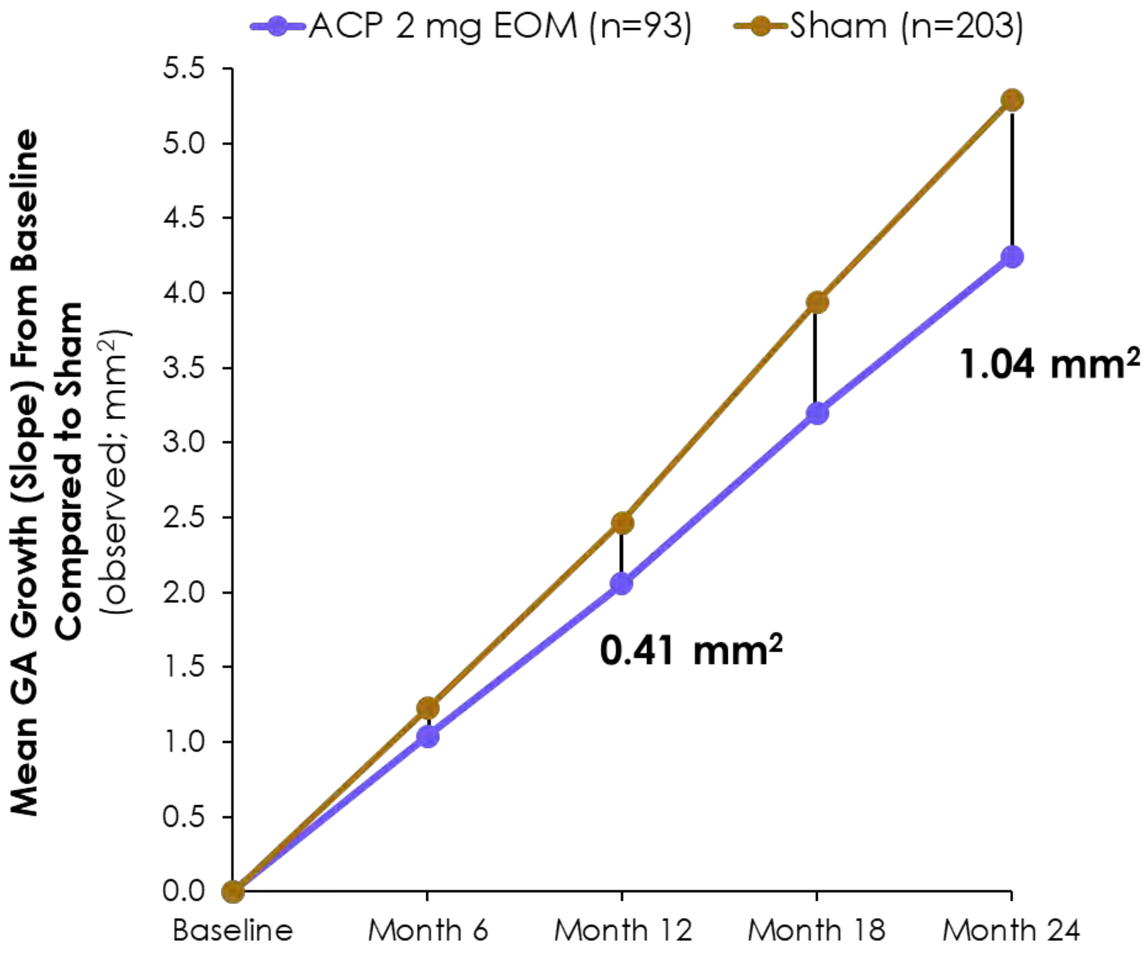
ACP 4 mg vs sham



Based on LSMEANS from MRM Model; ITT Population Hochberg procedure used for significance testing. *These least squares means are estimates of the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2 and should not be interpreted as directly observed data.

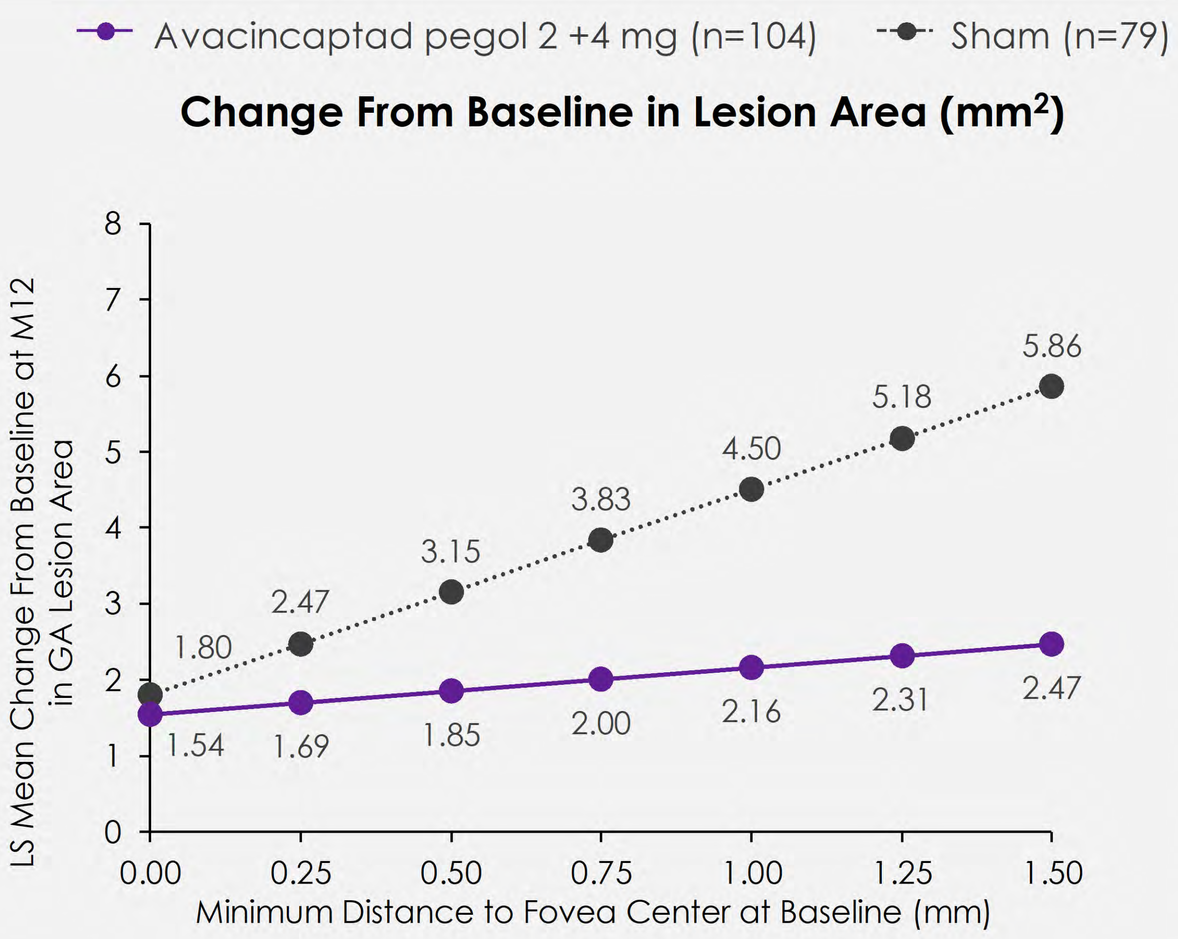
Early treatment effect observed by 6 months and increased over time through 2 years

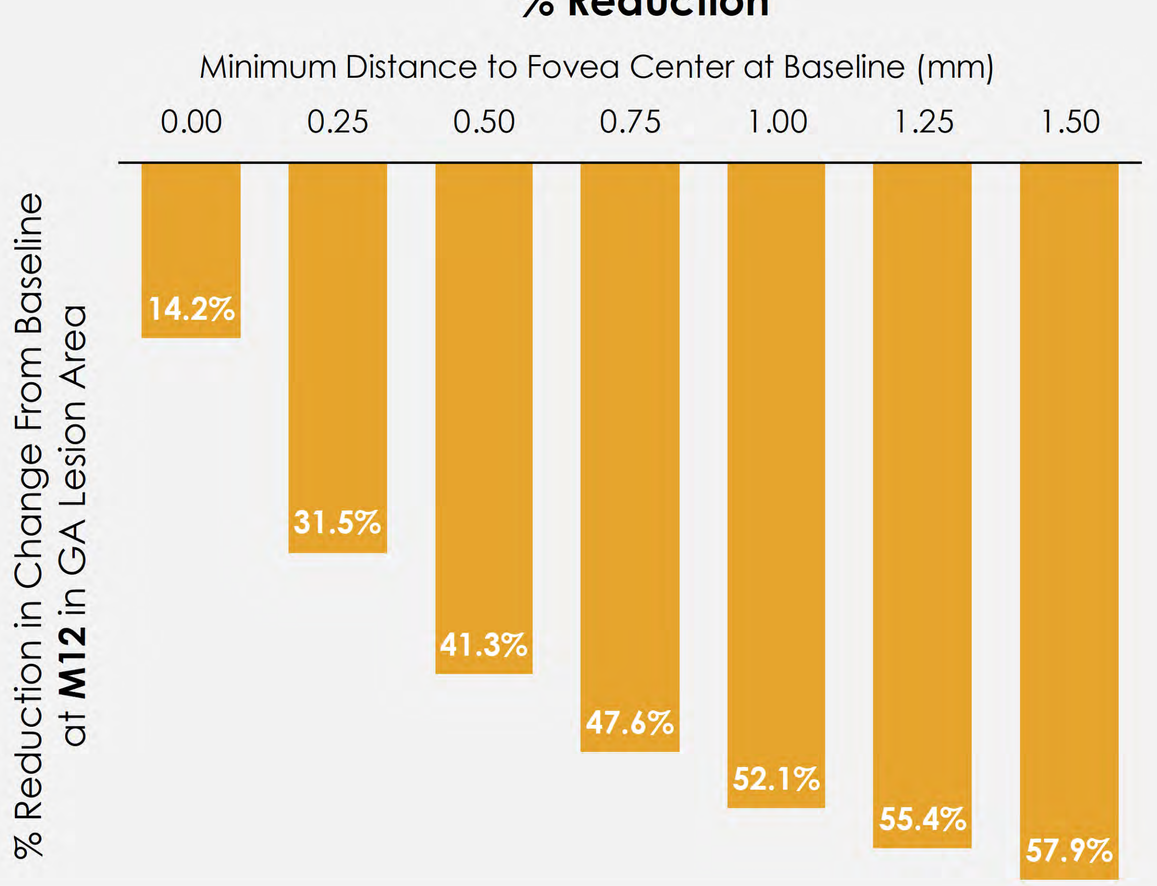




Note: This is a simplified piecewise slope spline MRM Analysis. The analysis is based on a mixed effects model for repeated measures assuming a piecewise linear growth slope every 6 months. The model included effects for treatment, time, and time by treatment interaction. The EOM group received monthly ACP 2 mg in the first year.
ACP, avacincaptad pegol; EM, every month; EOM, every other month.

Reduction based on lesion location (Month 12)





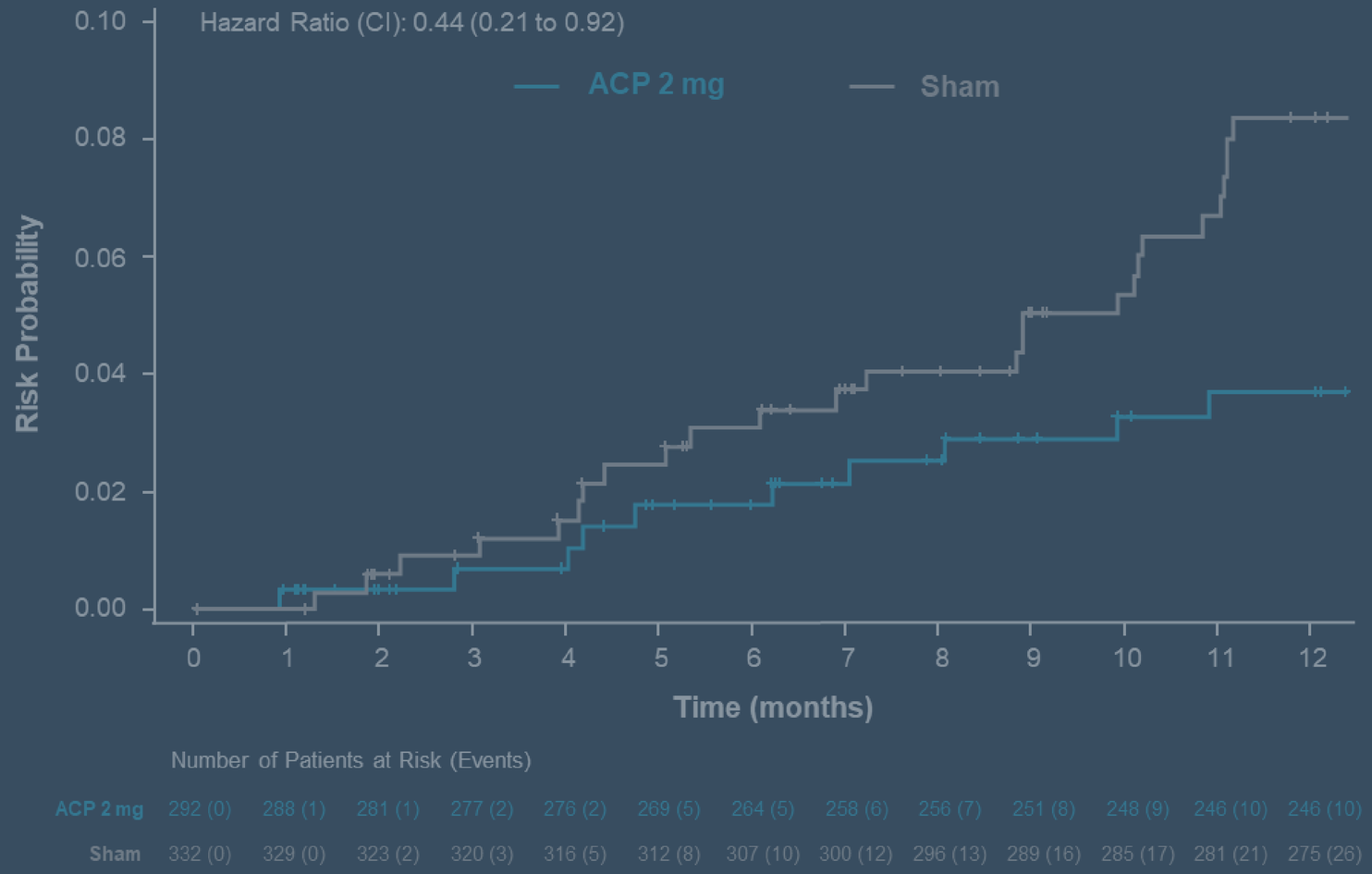
GA, geographic atrophy; LS, least square.
Jaffe GJ. Presented at: RWC. May 13, 2022.

Persistent Vision Loss and Photoreceptor Receptor Status (as Measured by EZ Attenuation) in the GATHER1 and GATHER2 Trials

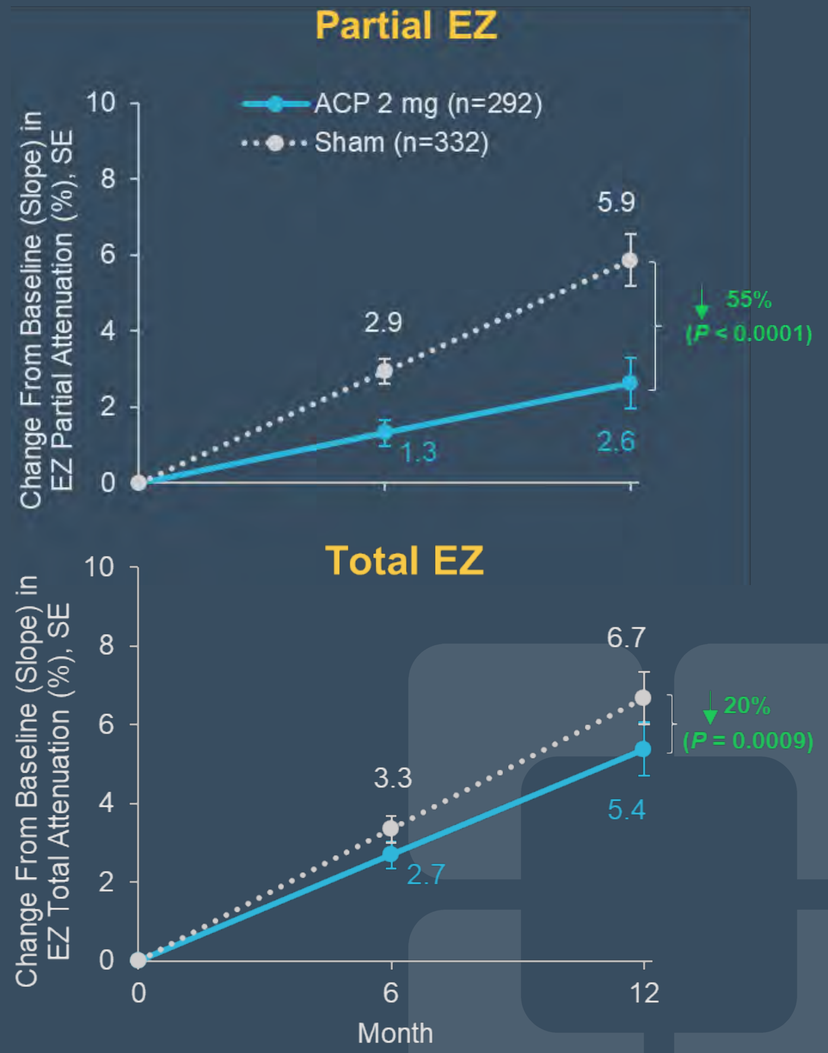
Pooled GATHER1 And GATHER2

56% risk reduction in persistent vision loss with ACP 2 mg vs sham over 12 months

≥15-letter loss in BCVA from baseline at any 2 consecutive visits (GATHER1 and GATHER2 pooled)



ACP 2 mg Reduced Both Partial and Total EZ Loss Compared to Sham Over 12 Months

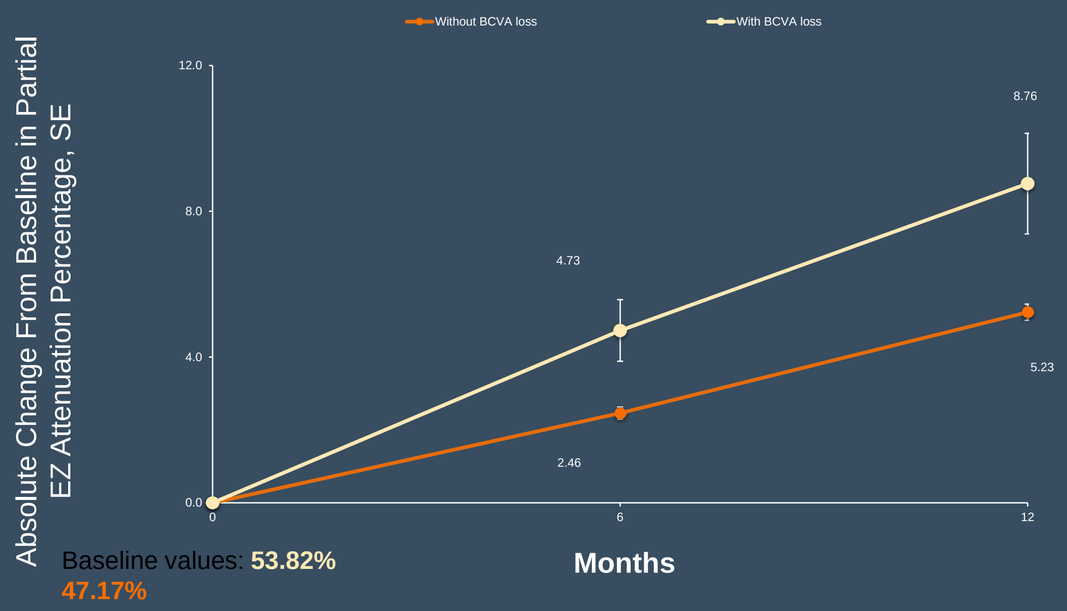


ACP, avacincaptad pegol; BCVA, best-corrected visual acuity; CI, confidence interval; SE, standard error.

Persistent Vision Loss* Is Associated with Greater Progressive EZ Loss

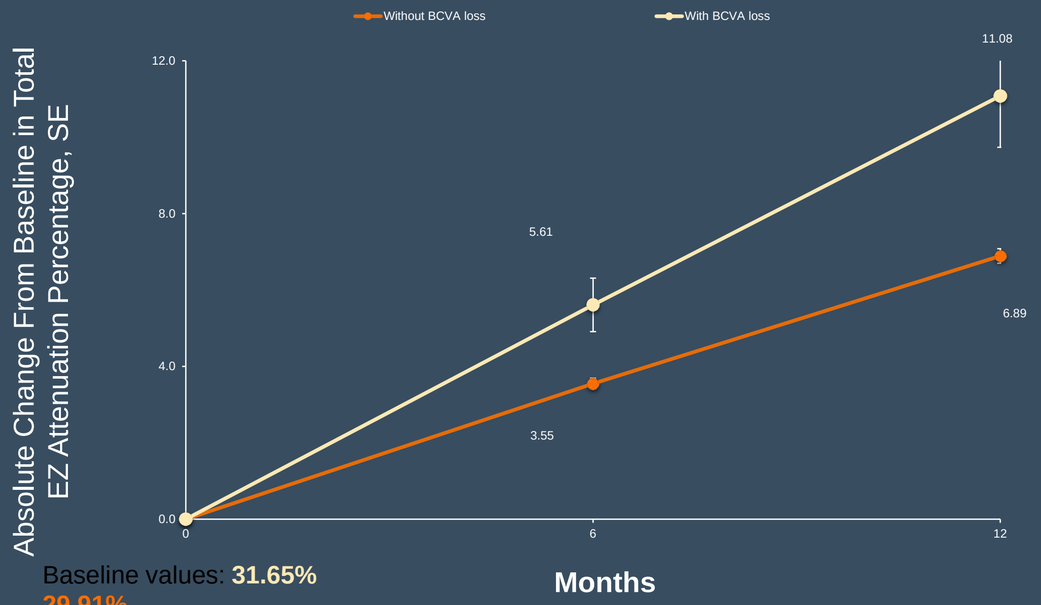
Pooled GATHER1 And GATHER2

Partial EZ



Baseline values: **53.82%**
47.17%

Total EZ



Baseline values: **31.65%**
29.91%

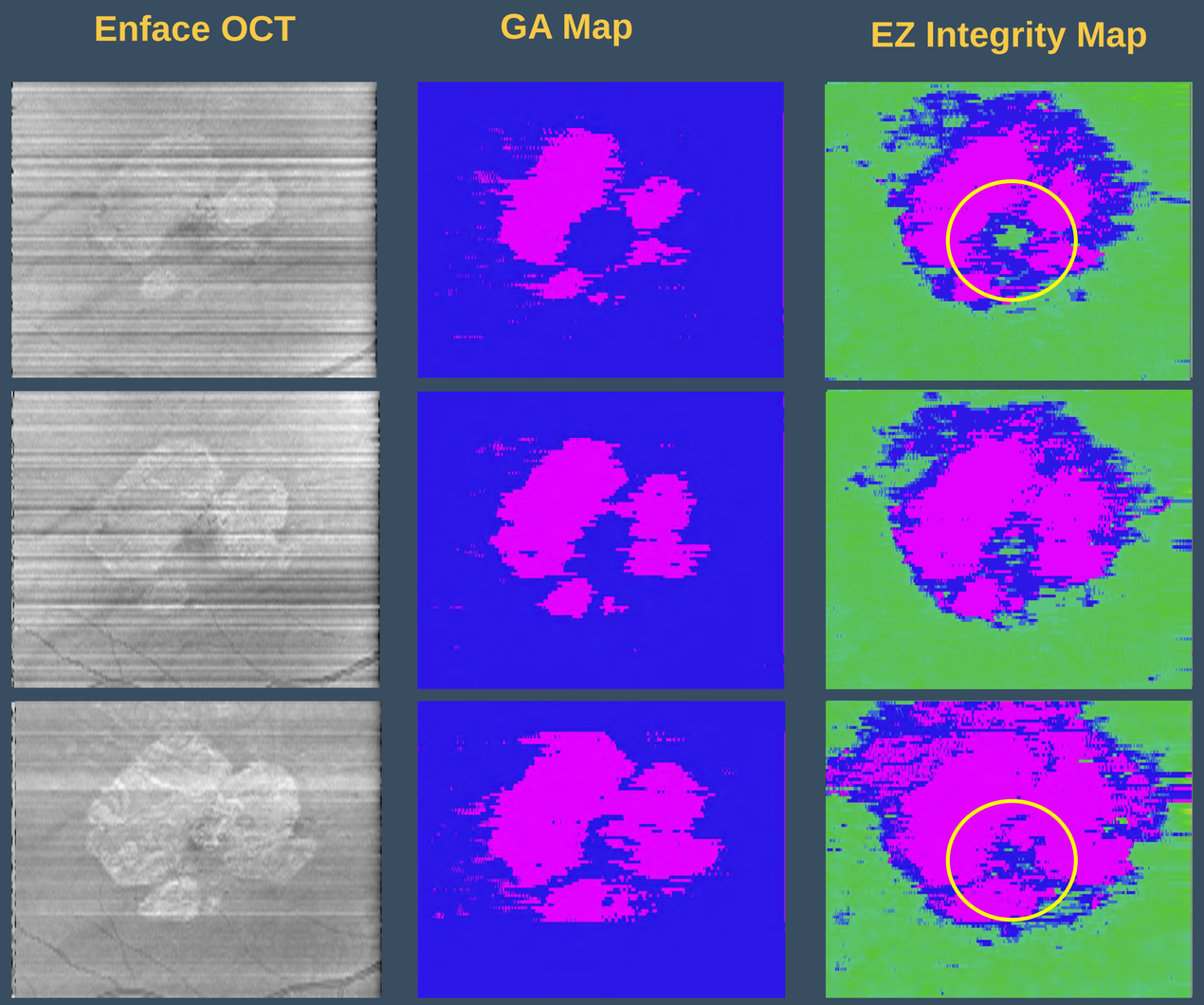
EZ-RPE – CST	Baseline	Change From Baseline at Month 12	Mean Percentage Reduction From Baseline at Month 12
With BCVA loss	4.83 µm	-4.21 µm	**87.2%**
Without BCVA loss	11.72 µm	-3.43 µm	**29.3%**

***Note: Persistent BCVA loss was defined as a loss of ≥15 ETDRS letters in BCVA from baseline at any 2 consecutive visits up to month 12.**

BCVA, best-corrected visual acuity; EZ, ellipsoid zone; RPE, retinal pigment epithelium; SE, standard error.

EZ Integrity and Vision Loss

Case Example Demonstrating Stable VA and EZ Integrity

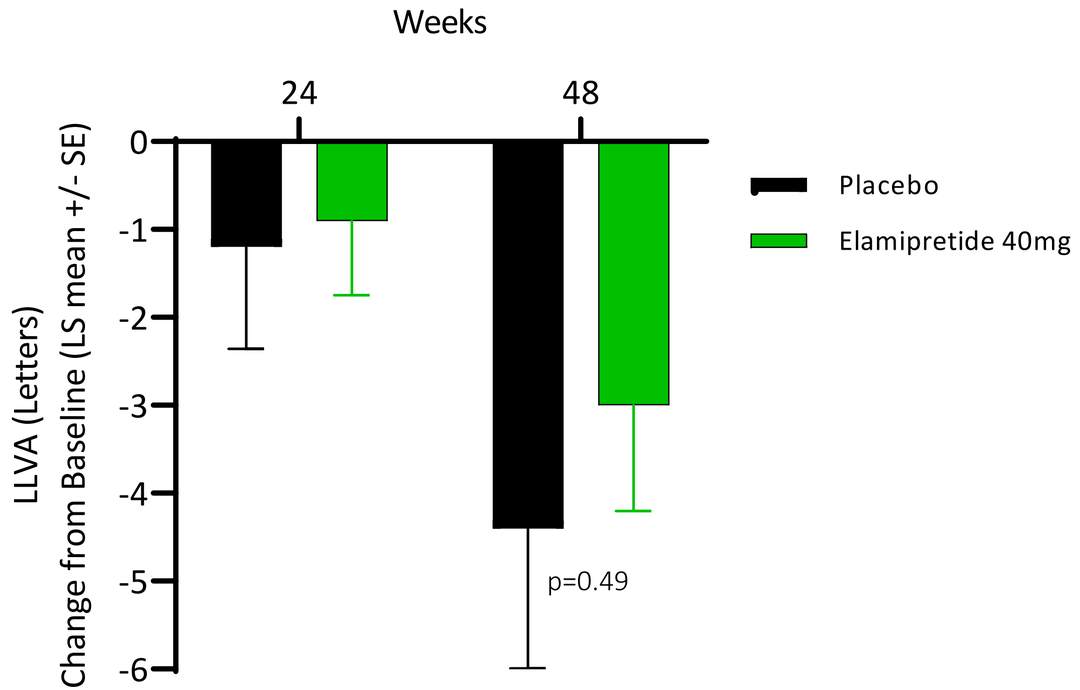


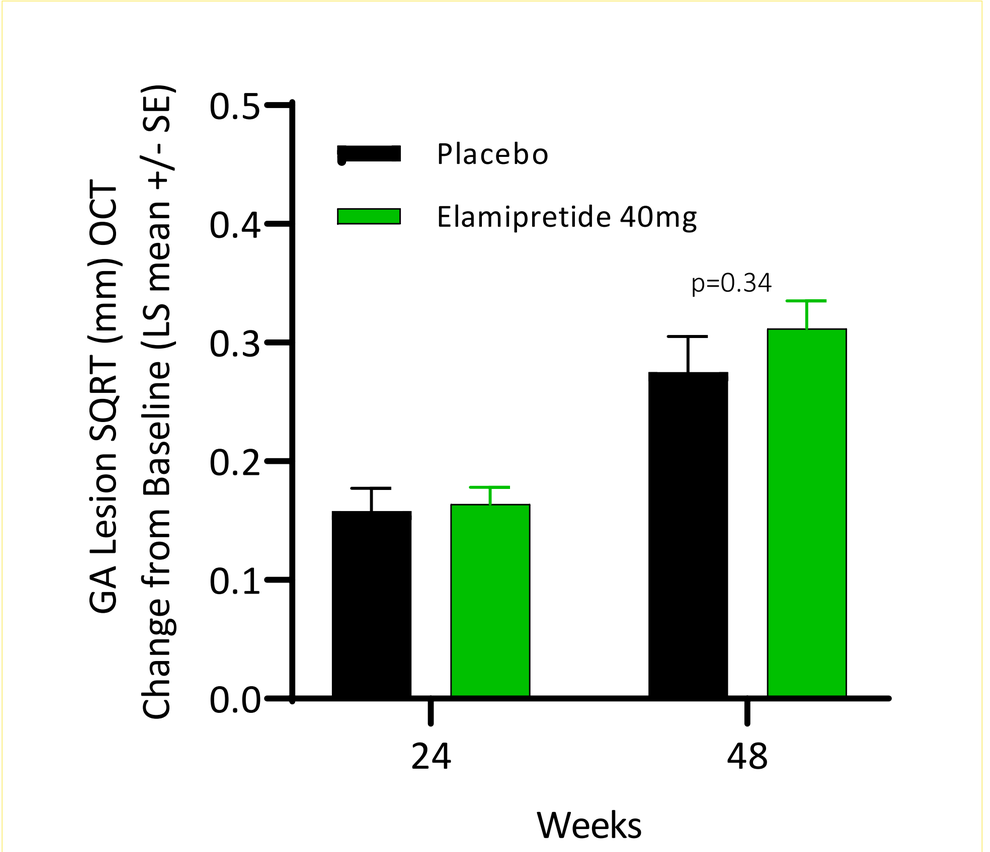
BCVA, best corrected visual acuity; GA, geographic atrophy; EZ, ellipsoid zone; OCT, optical coherence tomography; VA, visual acuity.

ReCLAIM-2 Trial Design

ReCLAIM-2 Primary Endpoint Family

*Primary endpoints of mean change in LLVA and GA progression measured by OCT were **not significant***

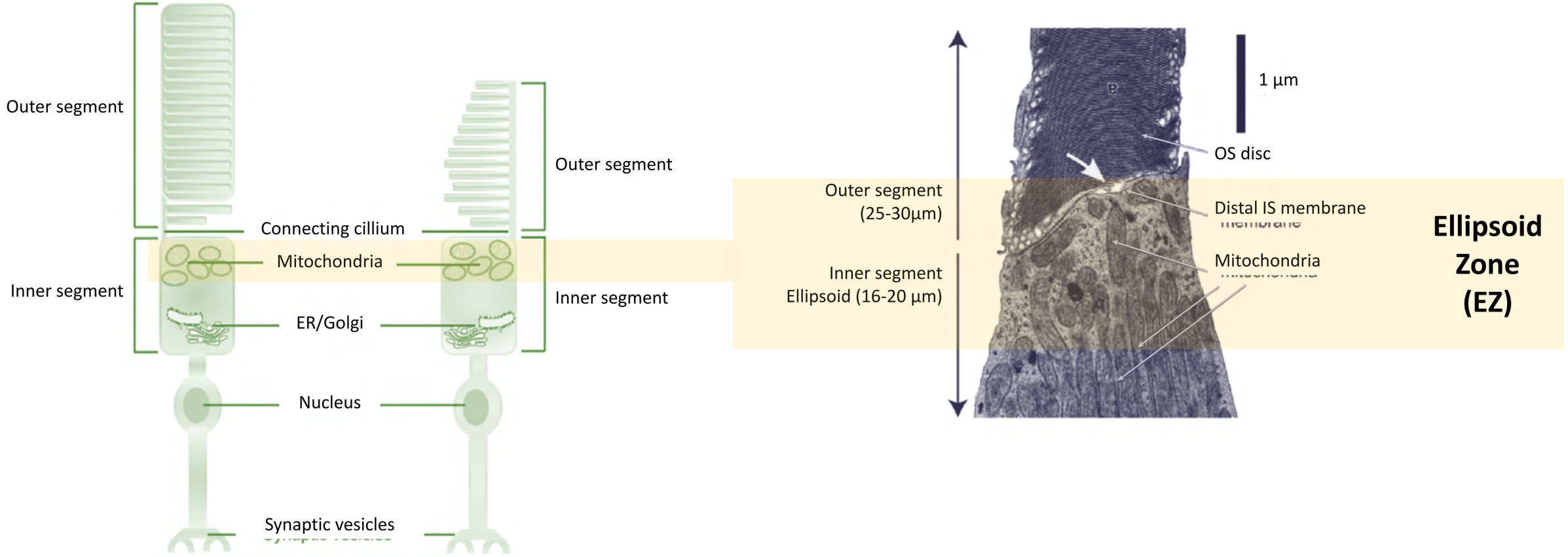




Least Square (LS) means estimated from a mixed-effects model for repeated measures (MMRM). The mITT population was used for the analysis, for LLVA, placebo n=52 and 48 for 24 and 48 weeks, respectively while elamipretide n=93 and 82, respectively. From GA assessment, placebo n=48 and 45, for 24 and 48 weeks, respectively while elamipretide n=89 and 76, respectively.

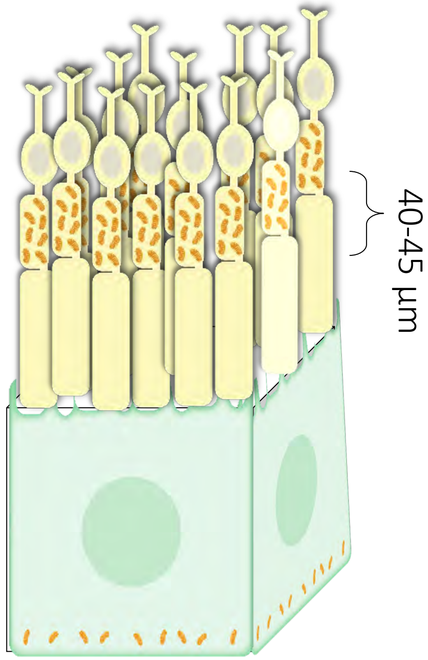
Why Focus on the Mitochondria-Rich Ellipsoid Zone (EZ)?

Progressive EZ damage precedes vision loss and RPE loss (GA) in patients with dry AMD[1,2]

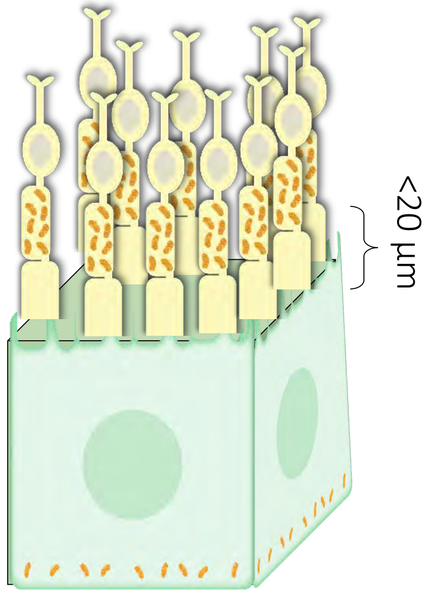


1. Pasricha MV. *Ophthalmol Retina*. 2021 May;5(5):396-408. 2. Sarici K. *Ophthalmic Surg Lasers Imaging Retina*. 2022 Jan;53(1):31-39.
Image: Fu Z. *J Lipid Res.* 2021;62:100035.

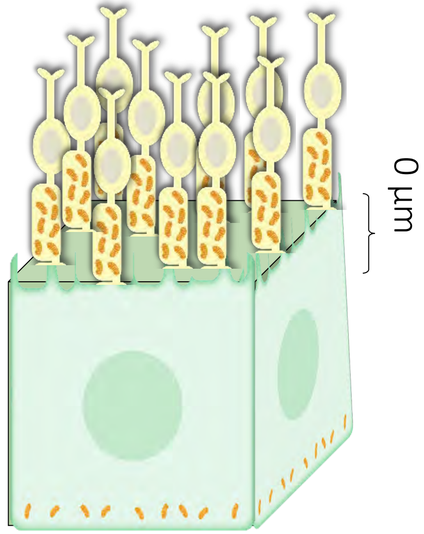
En Face Color Representation: EZ-RPE thickness



Normal
EZ to RPE
35-40 µm

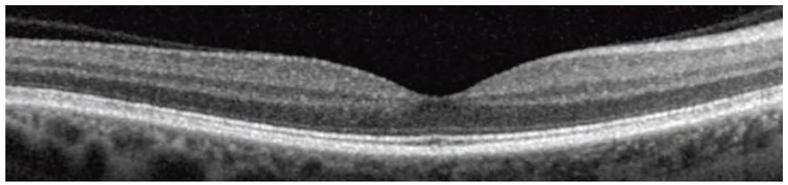


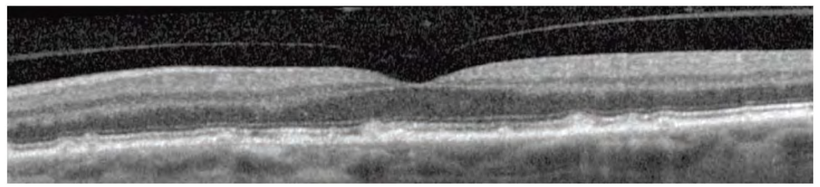
pEZa
EZ to RPE
<20 µm

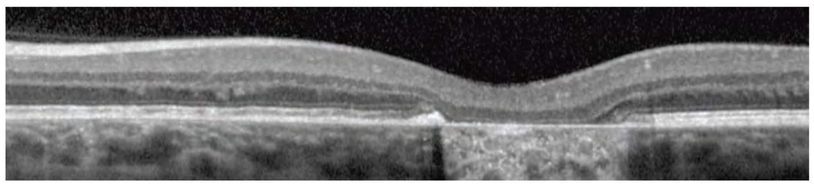


tEZa
EZ to RPE
0 µm

GA
EZ to BM
0 µm

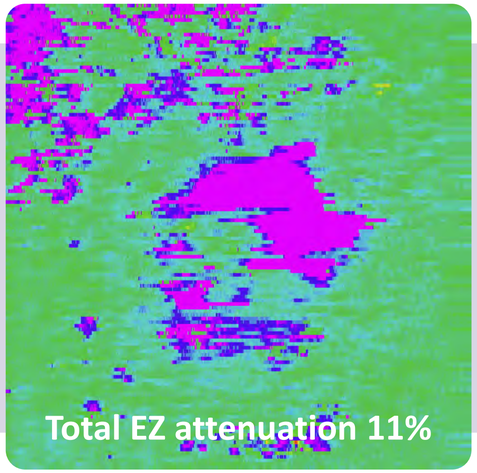
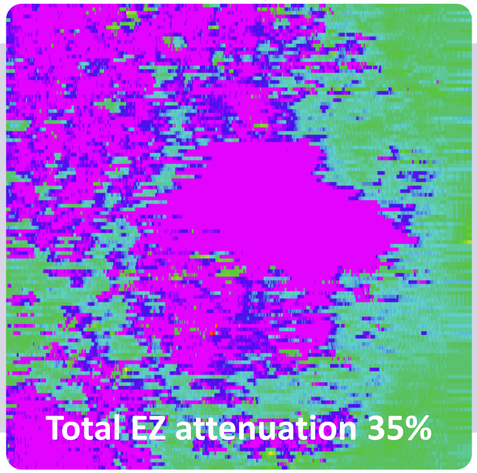
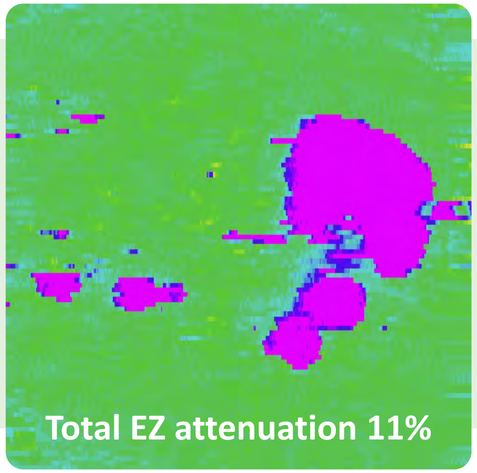
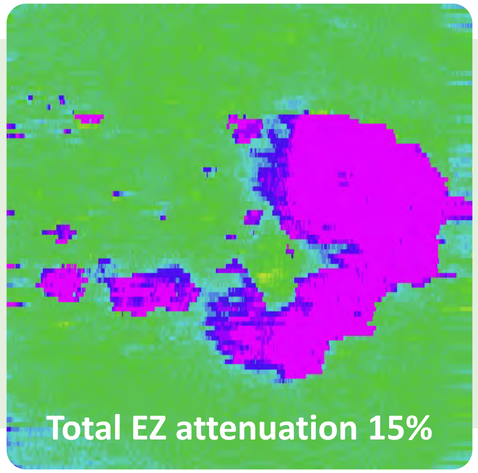


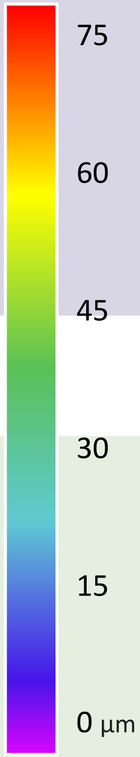




ReCLAIM-2: Elamipretide

Case study: Reduced EZ attenuation in a patient treated with elamipretide compared to placebo

	Baseline	Week 48	
Placebo SPIAM-xxx-xx-009			**-9 letters** change from baseline
Elamipretide SPIAM-xxx-xx-004			**+10 letters** change from baseline

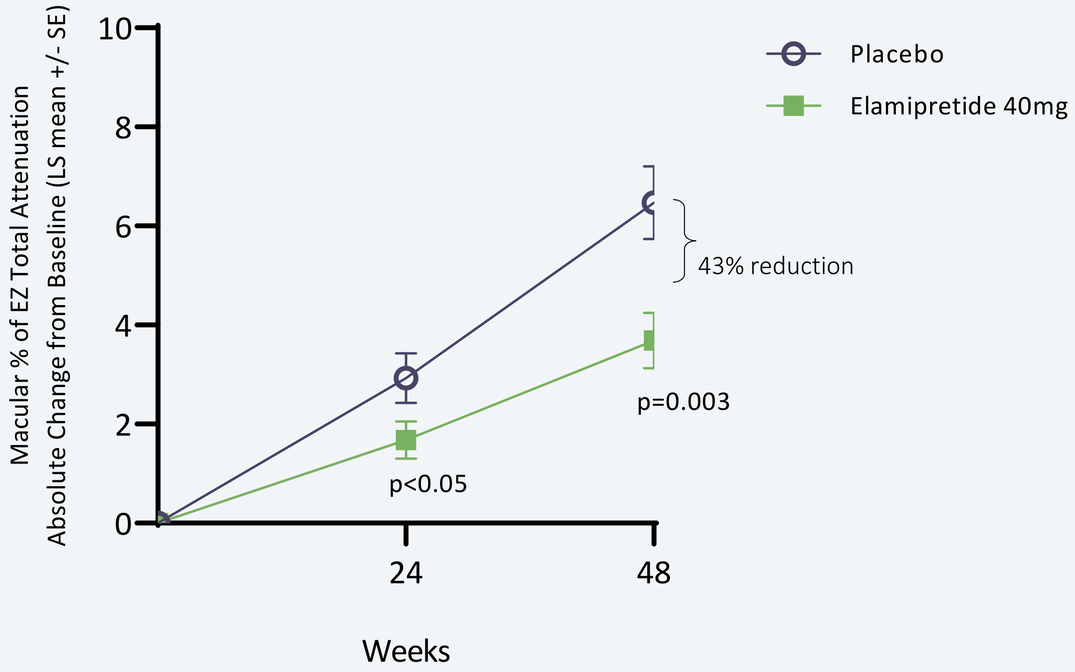


Stealth BIOTHERAPEUTICS

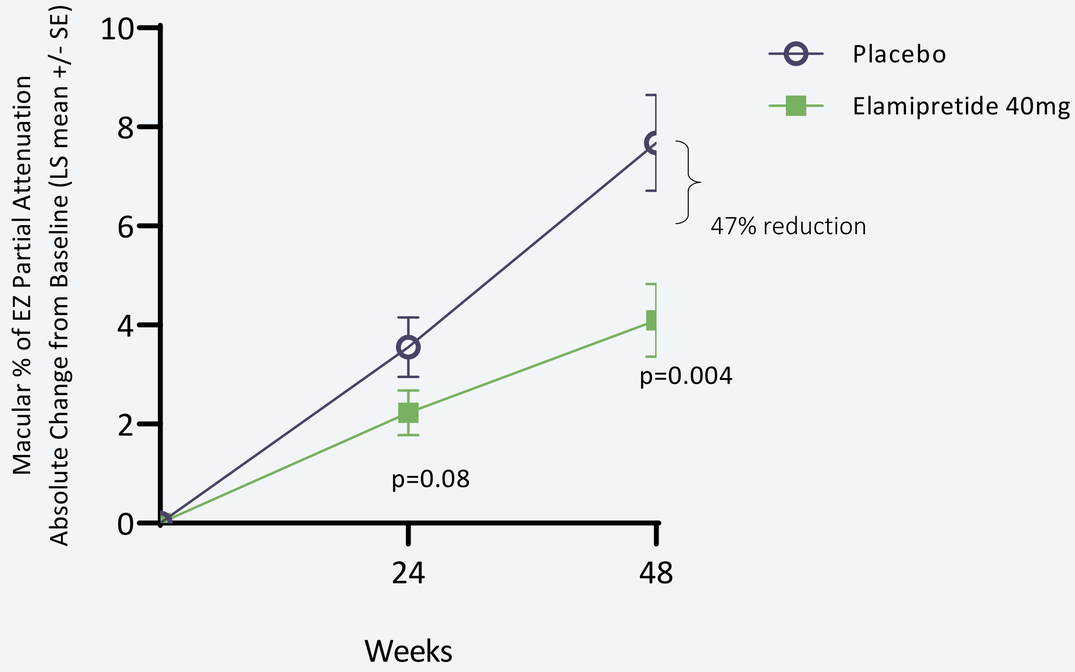
ReCLAIM-2 Phase 2: Elamipretide Reduced EZ Attenuation

Prespecified analysis provides proof of mechanism and elamipretide target engagement

EZ **Total** Attenuation: thickness of 0 µm on *en face* map



EZ **Partial** Attenuation: thickness of <20 µm on *en face* map



Least Square (LS) means estimated from a mixed-effects model for repeated measures (MMRM). The mITT population was used for the analysis; for Total Attenuation, placebo n = 50 and 42 for 24 and 48 weeks, respectively, while elamipretide n = 89 and 71, respectively. From Partial Attenuation, placebo n = 50 and 42, for 24 and 48 weeks, respectively, while elamipretide n = 89 and 71, respectively. Statistical analysis showing nominal “p values.”

Heier JS. Presented at the CTS meeting. 2022. Park City, UT.

Title Text

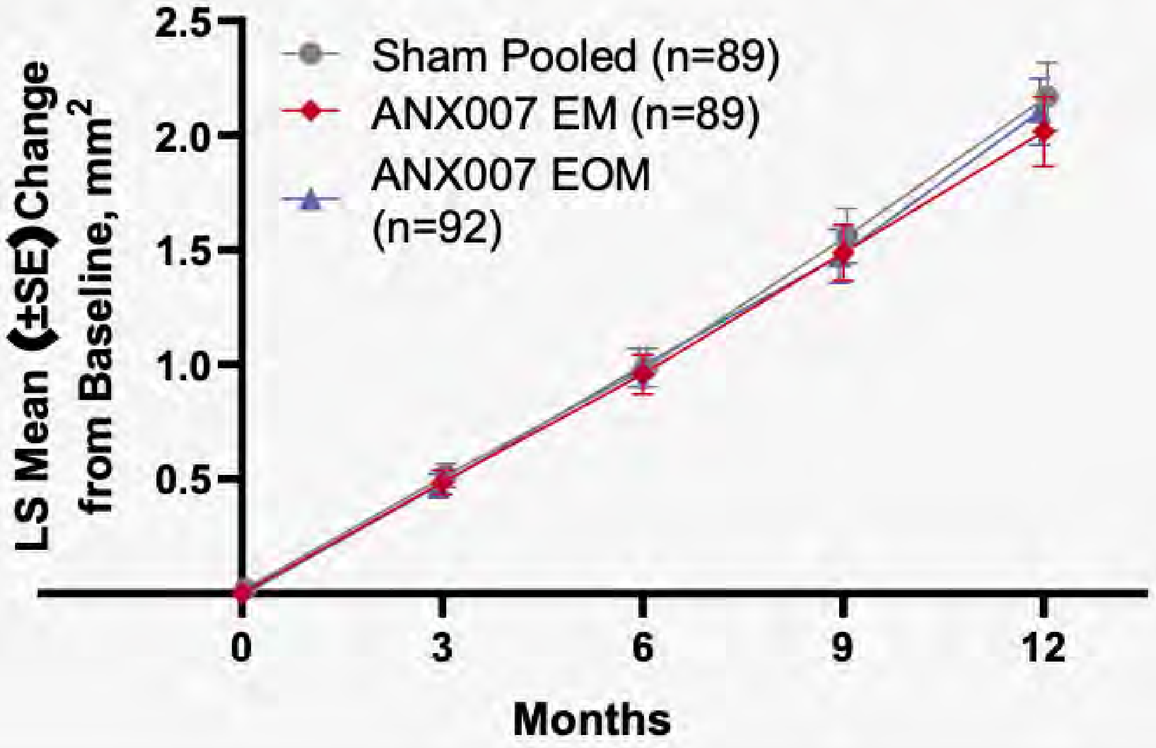
- Body Level One
  - Body Level Two
    - Body Level Three
      - Body Level Four
        - Body Level Five

Title Text

- Body Level One
  - Body Level Two
    - Body Level Three
      - Body Level Four
        - Body Level Five

Annexon Phase 2

GA Lesion Area Change from Baseline to Month 12+

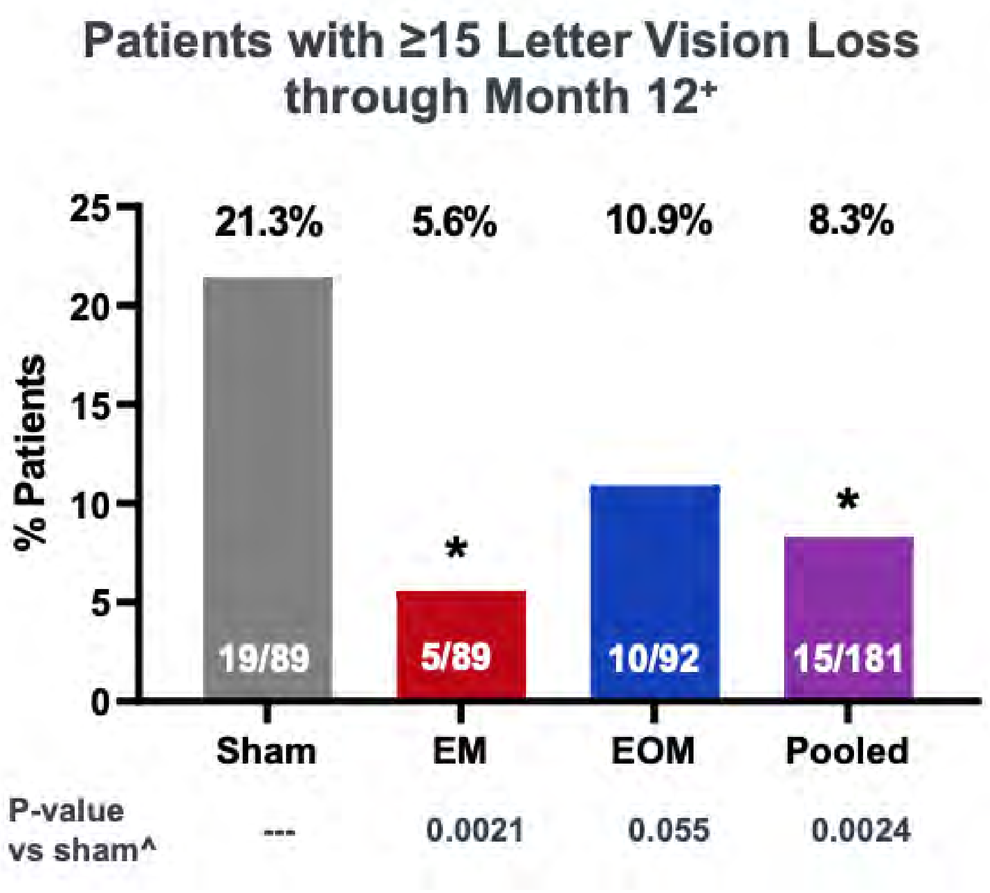


GA Area Change from Baseline at 12 Month

Arm	mm²	%	p-value
Sham	2.15	---	---
EM^	2.02	6.2%	0.526
EOM^	2.12	1.3%	0.896
ANX007 Pooled*	2.07	3.7%	0.673

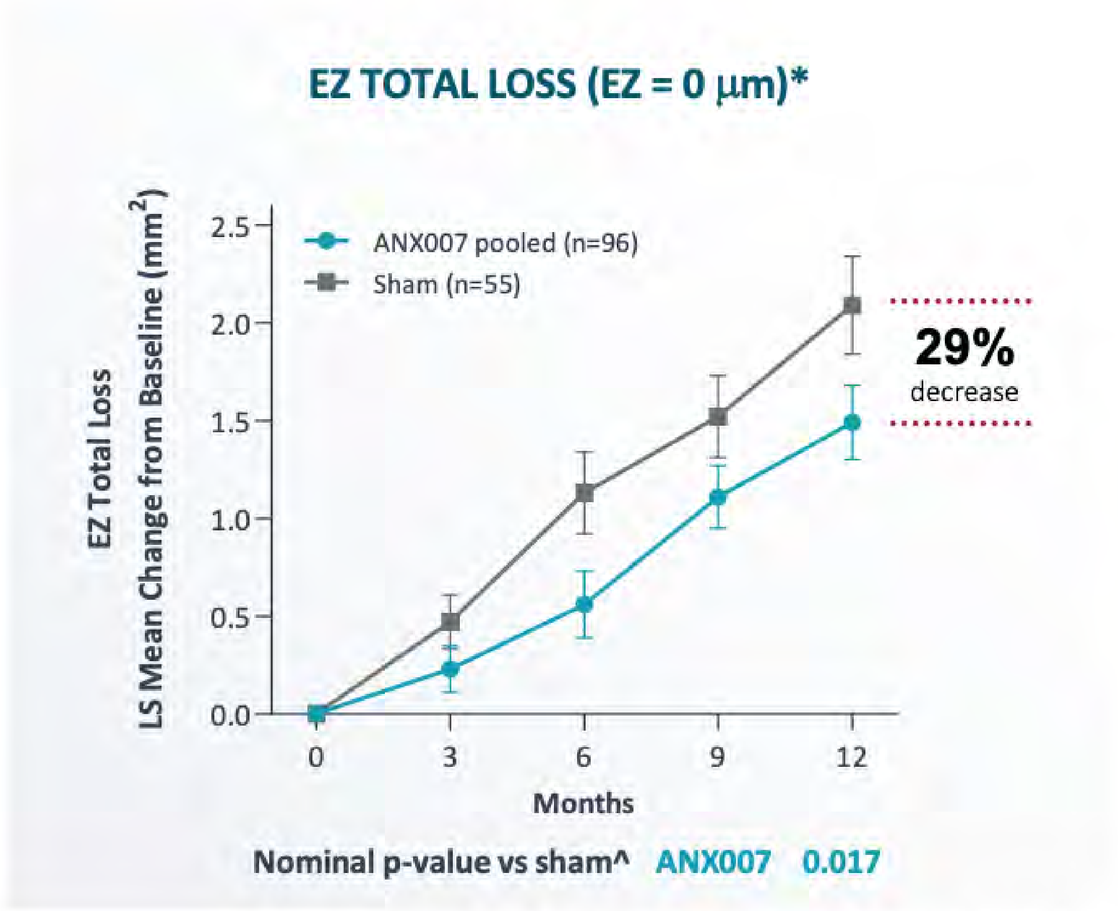
^3-arm MMRM model
*2-arm MMRM model

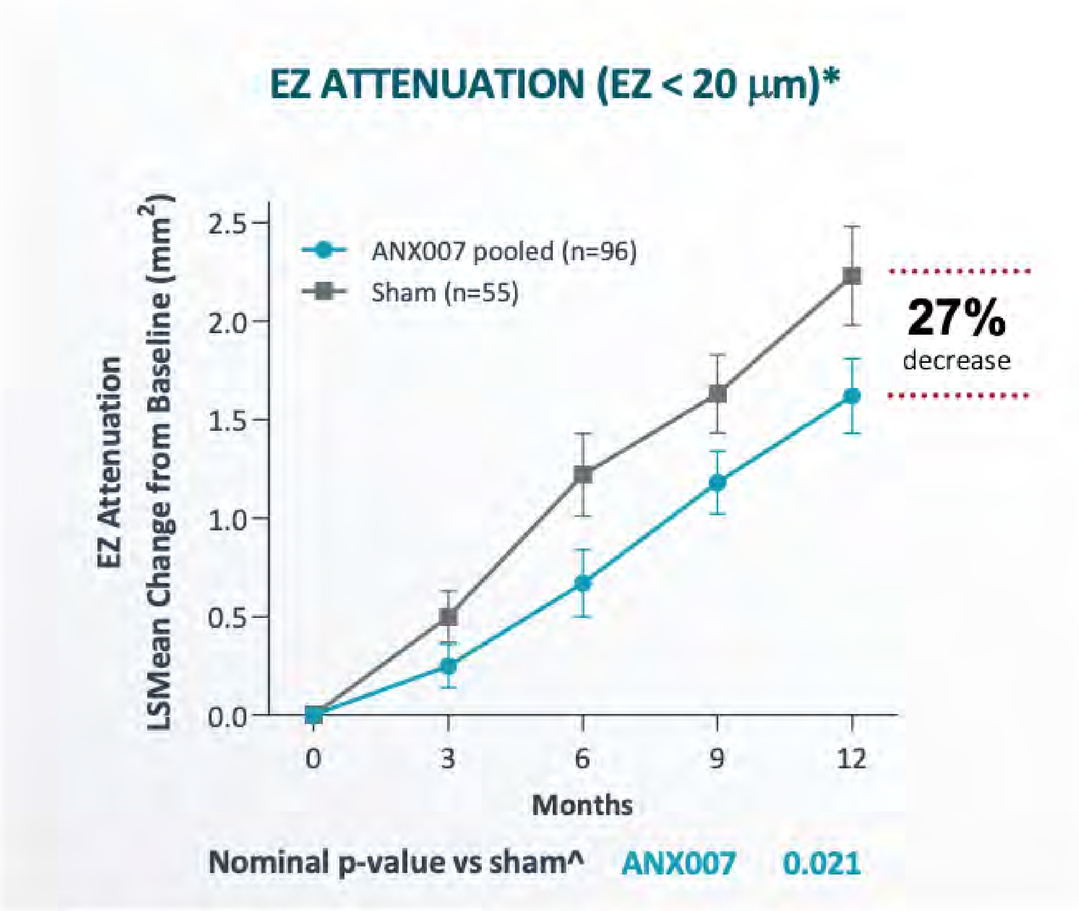
Annexon Phase 2b



- 15-letter loss: clinically meaningful endpoint
- Widely established functional endpoint
- Dose-dependent response
- Prespecified in ARCHER analysis

Annexon Phase 2b





^Nominal p-values from a mixed model for repeated measures (MMRM) analysis; Heidelberg Spectralis OCT population with baseline OCT data (n=151)
*Two treatment groups (EM and EOM) were not different statistically

Thank you...