

Structure–function link of ellipsoid zone integrity and low-luminance deficit in avacincaptad pegol-treated eyes with geographic atrophy

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KEY TAKEAWAYS

- LLD is strongly linked to photoreceptor health; greater baseline LLD is associated with worse LLVA and increased EZ attenuation
- ACP 2 mg reduced EZ attenuation progression (vs sham) over 18 months, with the greatest benefit observed in eyes with the highest baseline LLD
- EZ integrity and LLD may be potential biomarkers for disease progression and therapeutic response in GA

INTRODUCTION

- A better understanding of the structure–function relationship in GA is needed
- EZ integrity and LLD are markers of GA disease severity/progression:^{1–3}
 - LLD (BCVA minus LLVA) measures the eye’s ability to function in reduced luminance compared with normal light conditions.^{3,4} Greater baseline LLD has been linked to greater vision loss in GA^{3,5}
 - EZ integrity, an imaging biomarker of photoreceptor health observed on SD-OCT (Figure 1) has been linked to visual function in multiple retinal diseases, including GA^{1,6}

- In previous post hoc analyses, ACP 2 mg treatment resulted in:
 - Reduced BCVA loss and GA growth versus sham in eyes with the greatest baseline LLD (Figure 2)⁴
 - Reduced progression of EZ attenuation versus sham⁷

OBJECTIVE

- This post hoc analysis of GATHER1 and GATHER2 characterizes the relationship between structure and function by analyzing EZ integrity and LLD in eyes with GA treated with ACP 2 mg versus sham

Figure 1. EZ loss on SD-OCT

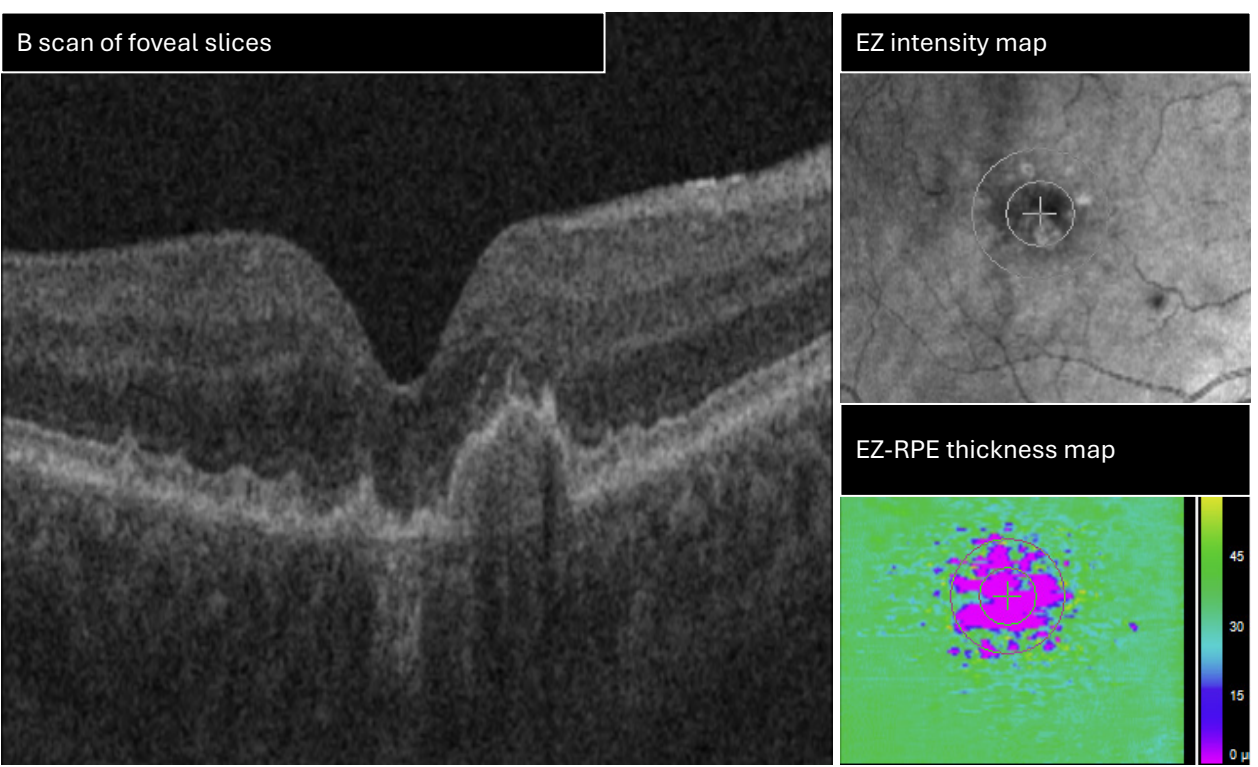
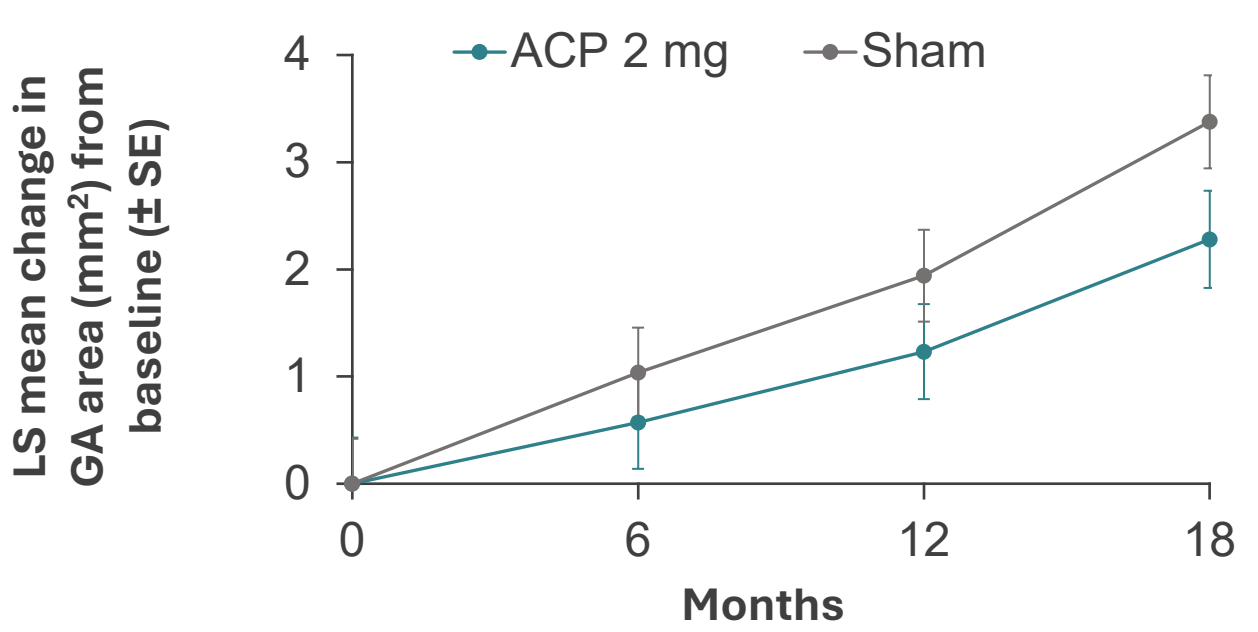


Figure 2. GA lesion growth in eyes with the greatest baseline LLD⁴



METHODS

Post hoc analysis of pooled GATHER1 and GATHER2

- GATHER1 (phase 2/3; NCT02686658) and GATHER2 (phase 3; NCT04435366) were multicenter, randomized, double-masked, sham-controlled trials that examined efficacy and safety of ACP 2 mg in patients with non–center point involving GA^{8,9}
- In both trials, BCVA was measured monthly. LLVA^a was measured monthly in GATHER1 and every 6 months in GATHER2^{8,9}
- Eyes in the ACP 2 mg and sham treatment groups were divided into quartiles according to baseline LLD and were designated as Q1 (lowest LLD) to Q4 (greatest LLD) (Table 1)¹⁰

Table 1. Post hoc analysis of pooled GATHER1 and GATHER2 data

Q1: Better visual function	Baseline LLD quartiles	ACP 2 mg (N=290)	Sham (N=330)	Combined (N=620)
	Quartile 1	≤16 letters	≤19 letters	≤18 letters (n=166)
	Quartile 2	17–26 letters	20–31 letters	19–29 letters (n=149)
	Quartile 3	27–46 letters	32–46 letters	30–46 letters (n=159)
	Quartile 4	≥47 letters	≥47 letters	≥47 letters (n=146)
Q4: Worse visual function				

SD-OCT analysis and measurement of EZ features

- SD-OCT scans were segmented using a proprietary machine-learning-enhanced multilayer retinal segmentation platform, followed by validation by certified readers
- The following EZ measures were extracted at baseline and up to 18 months for ACP 2 mg and sham groups in each LLD quartile

Total EZ attenuation/loss: ⁶ percentage of macular cube ^b with EZ-RPE thickness = 0 µm	Partial EZ attenuation/degradation: ⁶ percentage of macular cube ^b with EZ-RPE thickness ≤20 µm
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^aLLVA was measured after interposing a 2.0-log neutral-density filter to simulate a standard reduction in luminance.^{3,8,9}
^bSD-OCT images were obtained using 512 × 128 macular cube scan protocols with Cirrus systems (Carl Zeiss Meditec, Jena, Germany) or with 97-line volume scan (20° × 20°) protocols with the Spectralis system (Heidelberg Engineering, Heidelberg, Germany).^{8,9,11}

RESULTS

Table 2. At baseline, BCVA is balanced between LLD quartiles whereas LLVA is lowest in the quartile with the greatest LLD (Q4). BCVA and LLVA are balanced between ACP 2 mg and sham treatment arms

	LLD Quartile 1 (≤18 letters)		LLD Quartile 2 (19–29 letters)		LLD Quartile 3 (30–46 letters)		LLD Quartile 4 (≥47 letters)	
	ACP 2 mg (n=85)	Sham (n=81)	ACP 2 mg (n=73)	Sham (n=76)	ACP 2 mg (n=65)	Sham (n=94)	ACP 2 mg (n=67)	Sham (n=79)
BCVA letters, mean (SD)	71.7 (10.7)	69.9 (14.0)	71.6 (9.2)	74.2 (8.3)	69.1 (8.1)	68.9 (7.7)	70.3 (7.9)	70.6 (6.7)
LLVA letters, mean (SD)	60.2 (11.0)	57.7 (13.7)	48.0 (9.9)	50.2 (8.7)	30.9 (9.3)	31.0 (8.6)	14.6 (9.3)	14.0 (8.9)

Figure 3. Baseline EZ attenuation is numerically greater in eyes with greater baseline LLD. Baseline EZ measures were balanced between ACP 2 mg and sham treatment arms

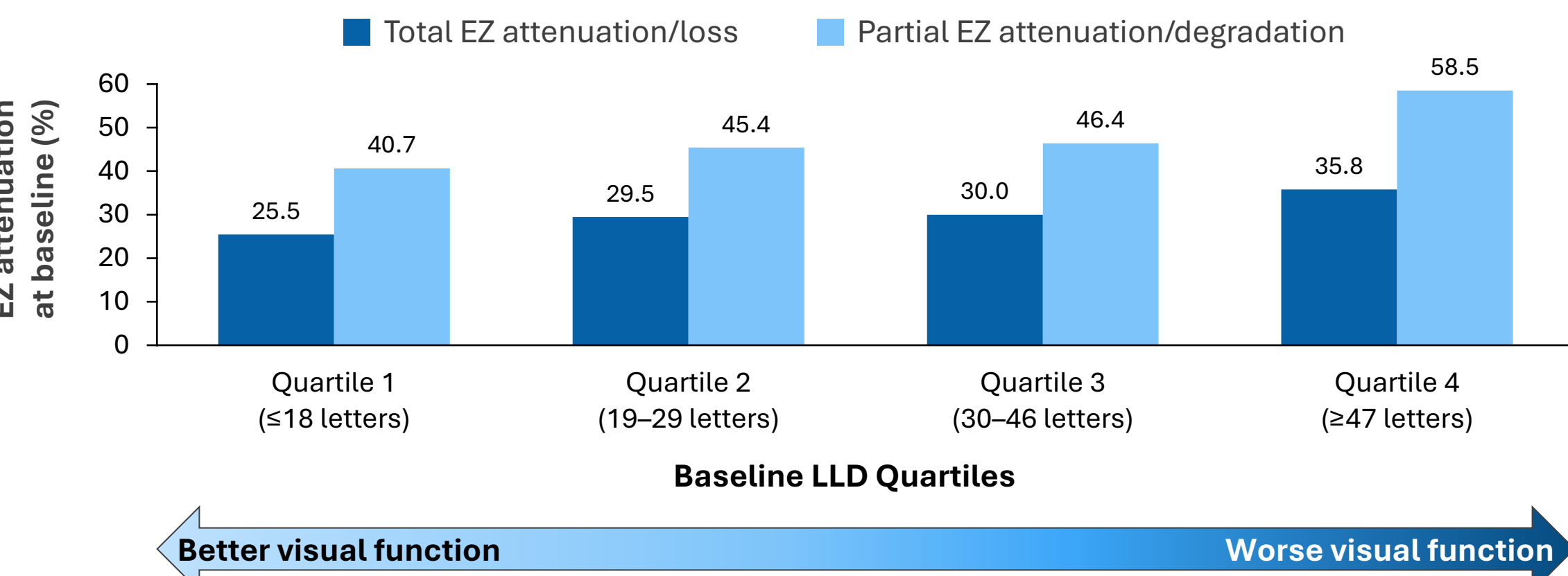


Figure 4. At month 18, ACP 2 mg reduced total EZ attenuation/loss vs sham, with the most pronounced benefit in eyes with the greatest baseline LLD (Q4)

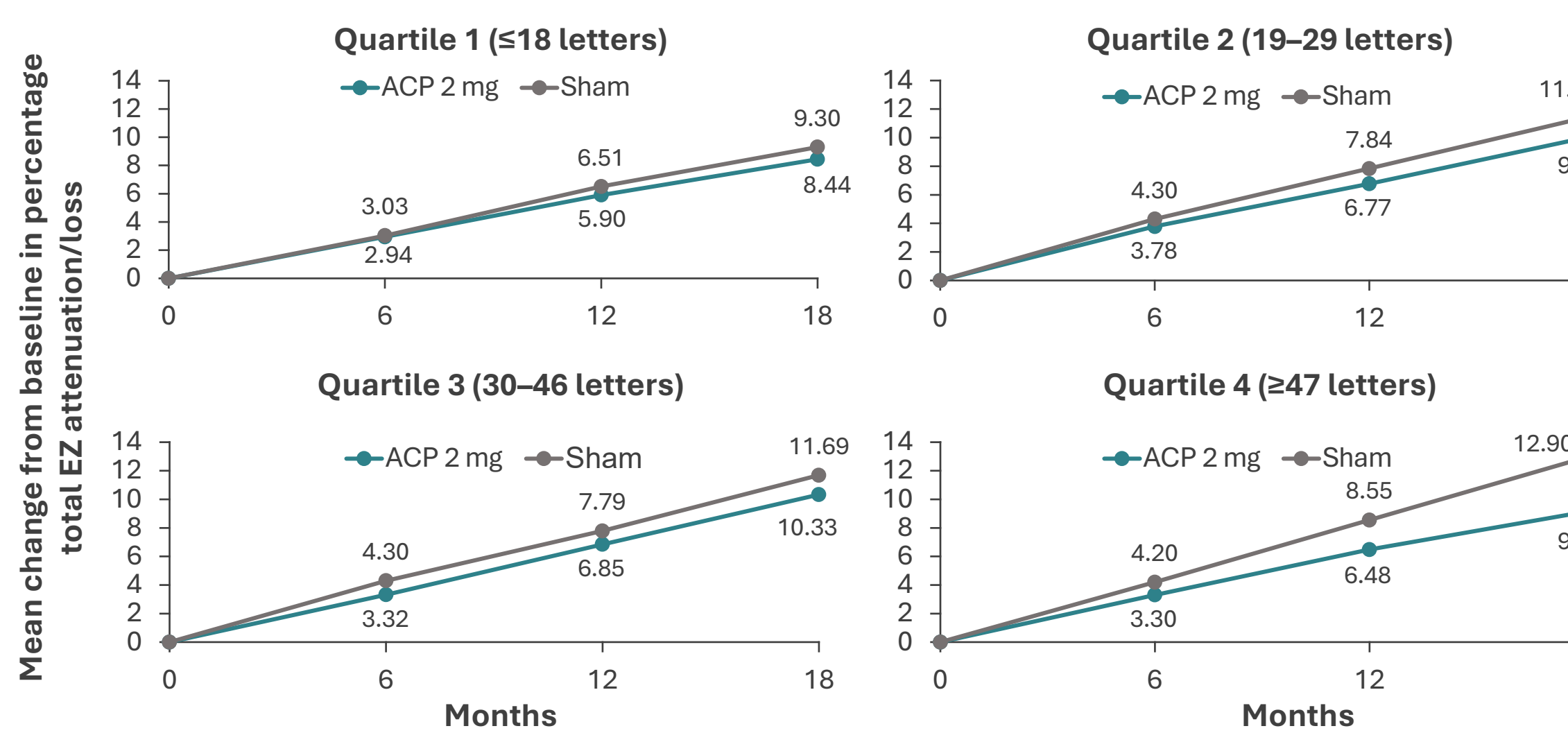
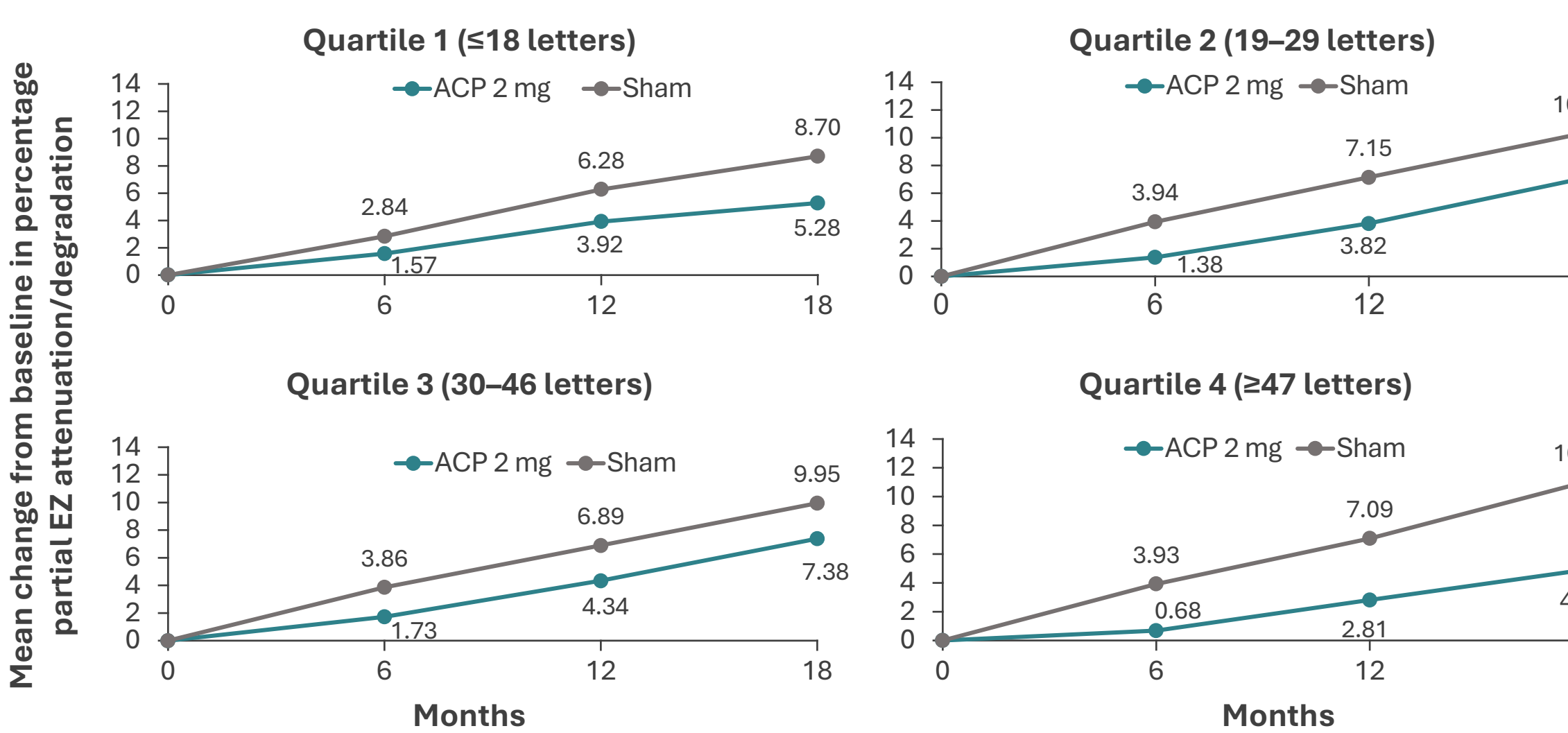


Figure 5. At month 18, ACP 2 mg reduced partial EZ attenuation/degradation vs sham, with the most pronounced benefit in eyes with the greatest baseline LLD (Q4)



CONCLUSIONS

- This post hoc analysis demonstrates a structure–function link in GA between photoreceptor health, measured by EZ integrity, and visual function, measured by LLD
- Eyes with greater baseline LLD tend to have worse LLVA and EZ attenuation at baseline than eyes with lower baseline LLD
- ACP 2 mg treatment reduced EZ attenuation progression versus sham over 18 months. This effect was most pronounced in eyes with the greatest baseline LLD, especially in reducing progression of partial EZ attenuation/degradation, which is considered an earlier indicator of photoreceptor damage
- Preservation of photoreceptors during early stages of loss with ACP 2 mg treatment may preserve vision in low light conditions
- These results support EZ integrity and LLD as potential biomarkers for disease progression and treatment response in GA. LLD may serve as a better measure of visual function in GA than BCVA



Abbreviations: ACP, avacincaptad pegol; BCVA, best corrected visual acuity; EZ, ellipsoid zone; GA, geographic atrophy; LLD, low-luminance deficit; LLVA, low-luminance visual acuity; LS, least squares; Q, quartile; RPE, retinal pigment epithelium; SD, standard deviation; SD-OCT, spectral-domain optical coherence tomography; SE, standard error.

References: 1. Abraham J, et al. Presented at ARVO; May 5–9, 2024; Seattle, WA, USA. Poster 5711–B0117. 2. Pfau M, et al. *JAMA Ophthalmol*. 2020;138(10):1026–1034. 3. Sunness JS, et al. *Ophthalmology*. 2008;115(9):1480–1488.e14882. 4. Bandello F, et al. Presented at: CoPhy; April 4–5, 2025; Seville, Spain. 5. Koester JM, et al. Presented at: ARVO; May 7–11, 2017; Baltimore, MD, USA. 6. Yordi S, et al. *J Pers Med*. 2024;14(5):543. 7. Ehlers JP, et al. Presented at: Angiogenesis; February 3, 2024; virtual. 8. Jaffe GJ, et al. *Ophthalmology*. 2021;128(4):576–586. 9. Khanani AM, et al. *Lancet*. 2023;402(10411):1449–1458. 10. Frenkel RE, et al. *Br J Ophthalmol*. 2016;100(8):1052–1057. 11. Ehlers JP, et al. *Transl Vis Sci Technol*. 2021;10(3):29.

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