Unlocking Structure/Function Relationships in Dry AMD/GA: Central Subdomain Preservation and Visual Acuity Protection with C1q Inhibition

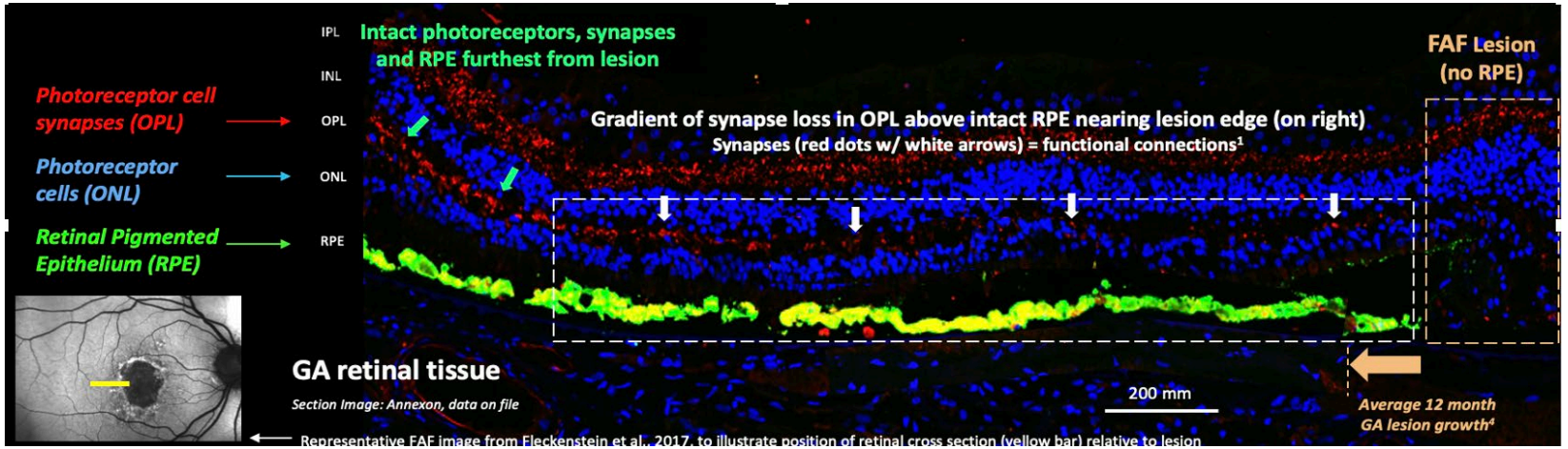
Jeffrey Heier, *Glenn Jaffe, Eleonora Lad, Karl Csaky, Charles Wykoff, Paolo Eduardo Stanga, Scott Borland, Alessia Tassoni, Ted Yednock and Lori Taylor*

FloRetina Meeting 2024

Photoreceptor Cells and Synapses Loss Outside of GA Lesion

Human GA Retina

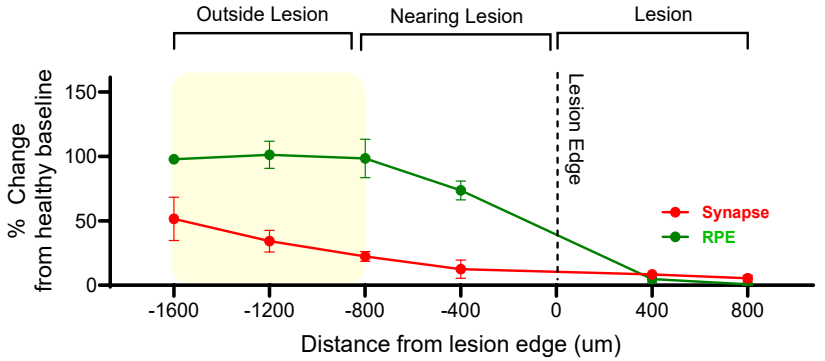
- Gradient of photoreceptor synapse and cell loss above intact RPE nearing lesion edge (white box)
- Photoreceptors are lost prior to RPE[1]; Loss of synapses is loss of function[2]
- FAF lesion growth tracks RPE loss, not photoreceptors, and correlates poorly w/ visual function[3]



Gradient of synapse loss above intact RPE nearing lesion edge

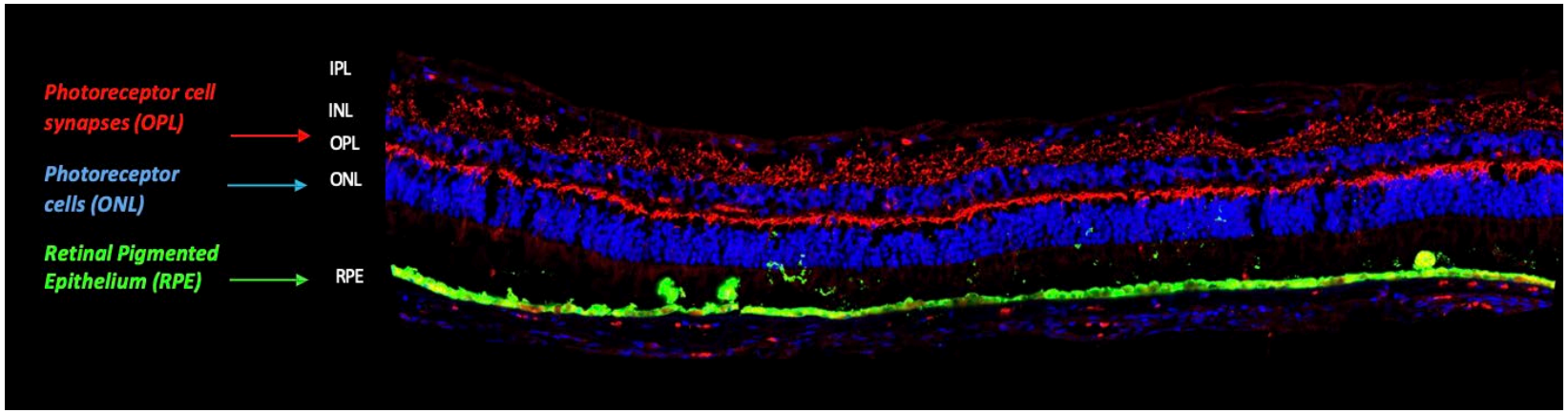
Photoreceptor Synapses
< 50% decrease outside lesion boundary

RPE cells integrity
intact in area of synaptic loss

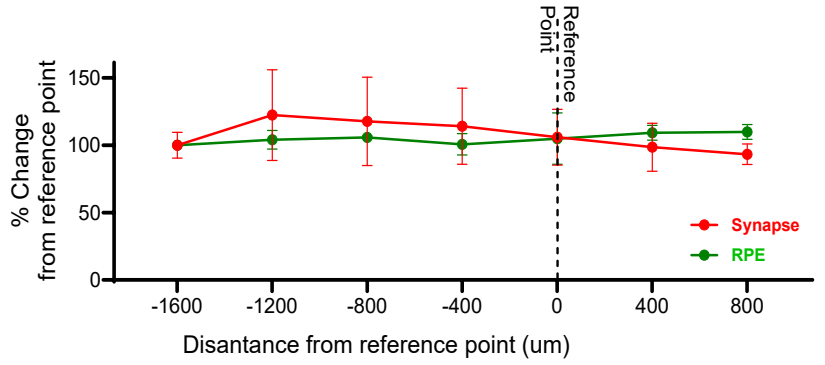


Healthy Human Retina

- Uniform layers of photoreceptor cells and synapses



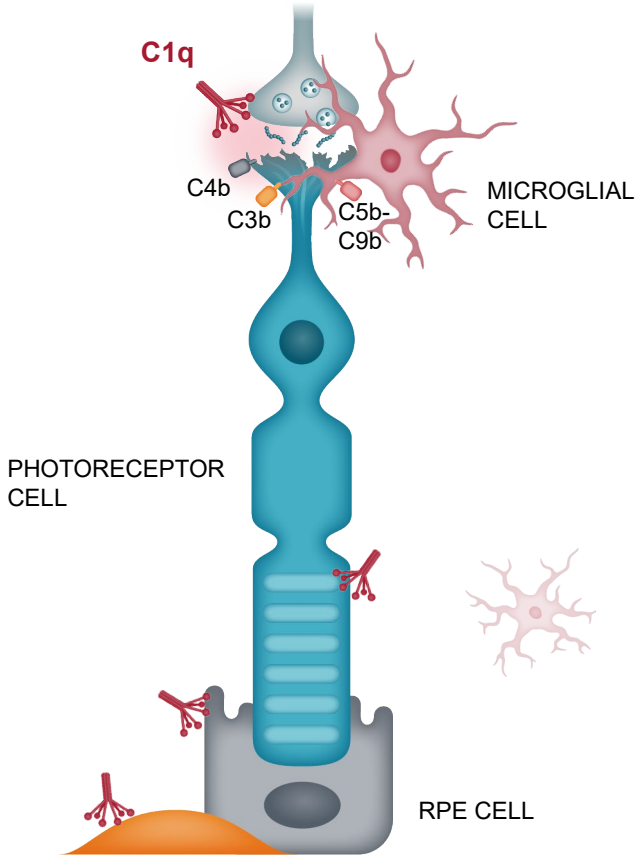
Consistent synapse and RPE integrity across healthy retina



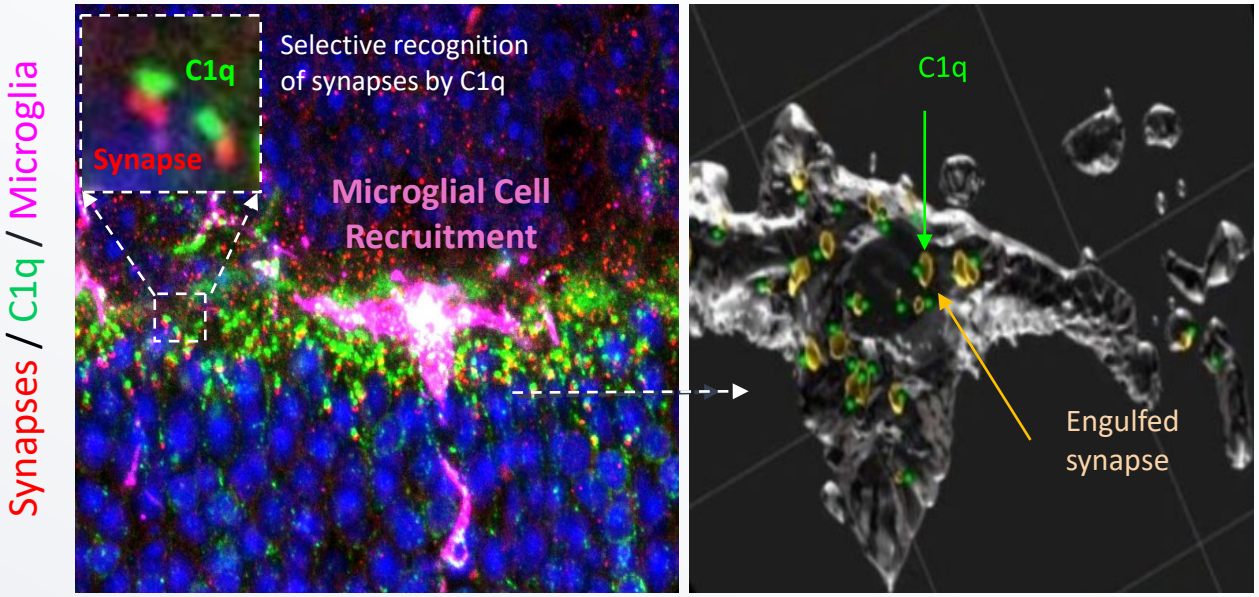
[1]Bird et al., 2014 *JAMA Ophthalmol* doi:10.1001/jamaophthalmol.2013.5799; Li, et al., 2018 *Retina* 38:1937; Pfau, et al., 2020 10.1001/jamaophthalmol.2020.2914; Sarks, et al., 1988 *Eye* 2:552; [2]Selkoe, 2002 doi: 10.1126/science.1074069; Burger, et al., doi.org/10.1016/j.ydbio.2021.04.001; [3]Heier, et al., 2020 Ophthalmology Retina **4**:673; [4]Shen, et al., 2020 *Ophthalmol Retina* **4**:899

Rationale for C1q in GA: C1q Drives Synapse Destruction and Removal by Microglia in a Model of Photoreceptor Degeneration

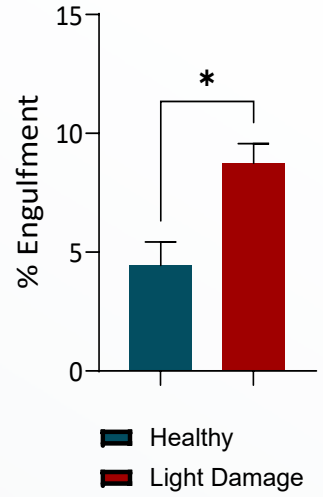
C1q binds stressed photoreceptor synapses and tags them for removal by microglia cells



MICROGLIAL ENGULFMENT OF C1Q-COATED SYNAPSES

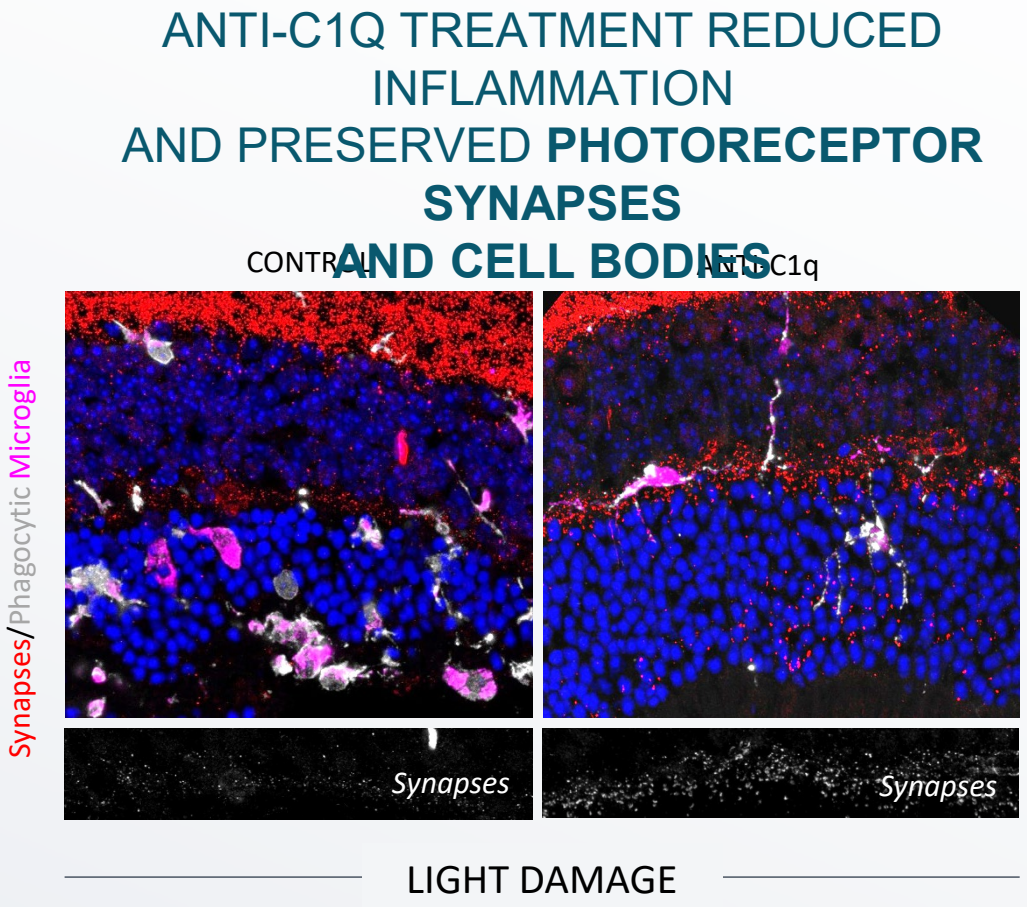


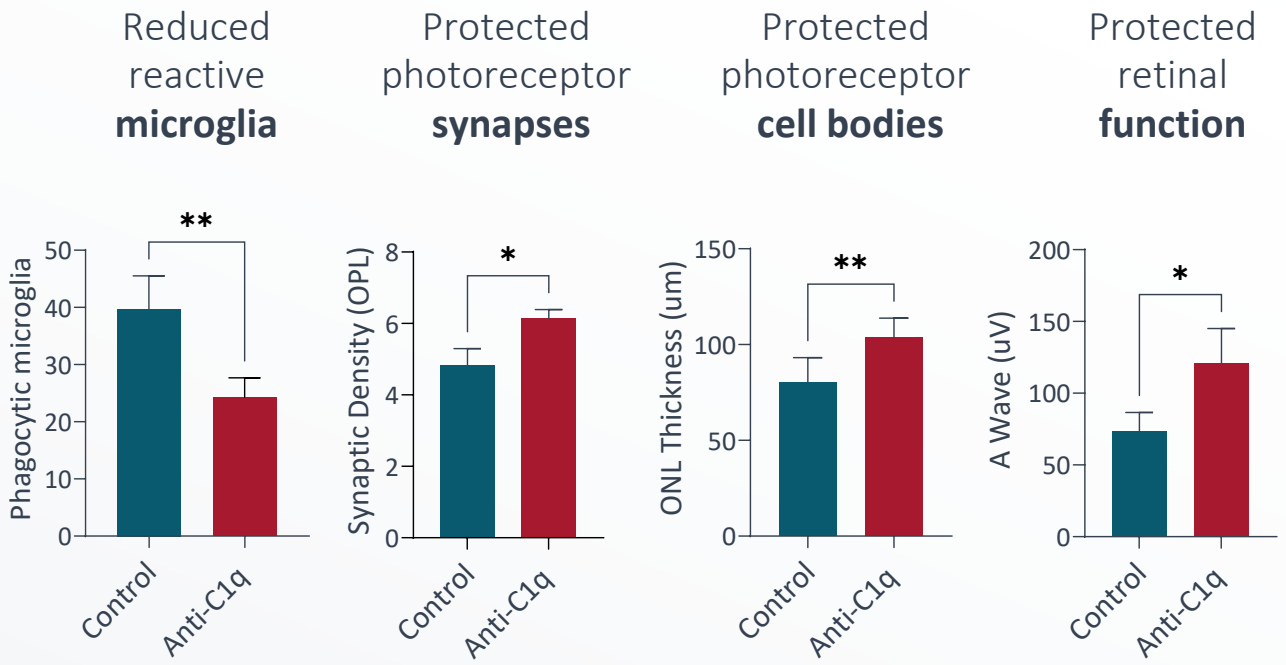
Increased engulfment of synapses by microglia



Tassoni, et al., ARVO, 2024 and Annexon on file

Rationale for C1q in GA: Anti-C1q Protected Photoreceptor Cells and Function in Models of Photoreceptor Damage

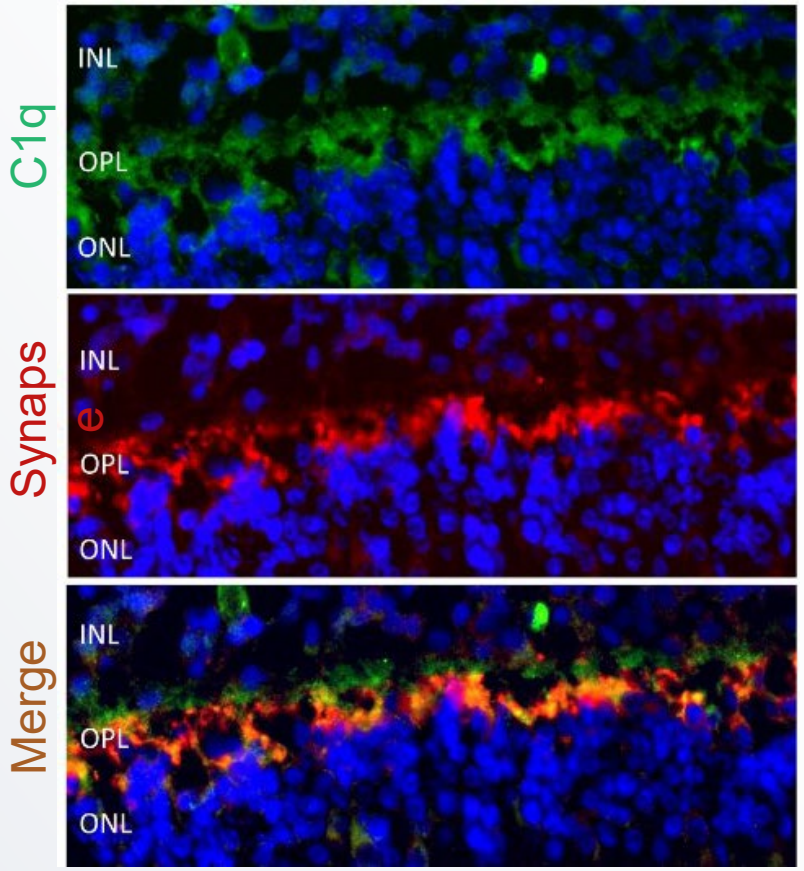




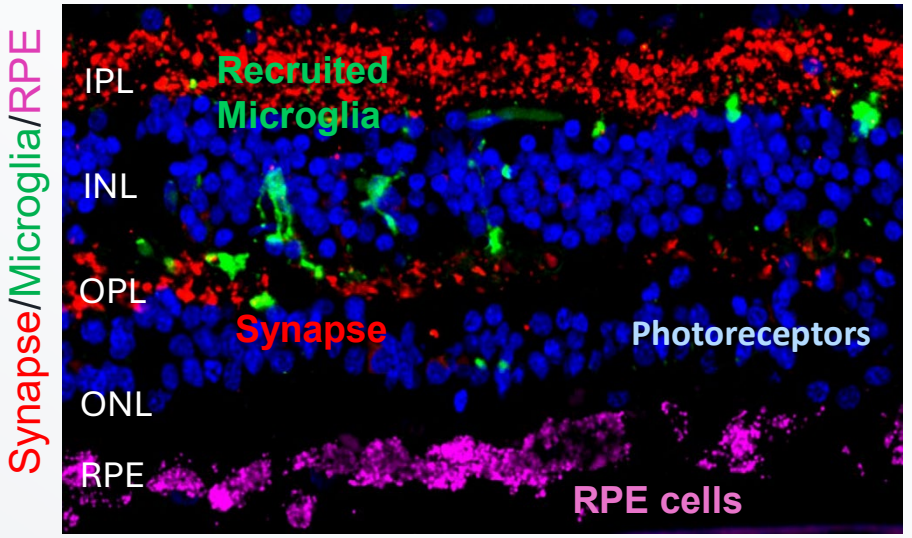
Tassoni, et al., ARVO 2024; Annexon data on file; Jiao, et al., 2018 *Mol Neurodegener* **13**:45;.

Evidence of C1q in Human GA: C1q Deposition on Photoreceptor Synapses and Microglia Recruitment in Postmortem GA Retinal Tissue

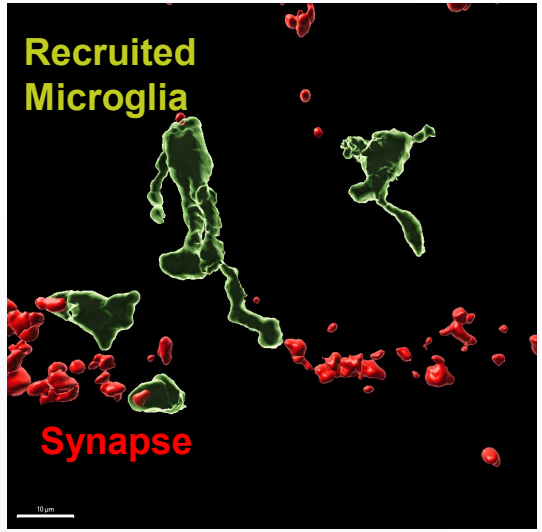
C1Q DEPOSITION ON PHOTORECEPTOR SYNAPSES



MICROGLIA RECRUITMENT AND **PHOTORECEPTOR SYNAPSE LOSS** IN POSTMORTEM GA RETINA TISSUE



Microglial Recruitment and Synapse Engulfment



Tassoni, et al., ARVO 2024; Annexon data on file;

ARCHER: Phase 2 Trial of C1q Inhibitor ANX007 in GA Patients

ANX007, non-pegylated IVT-administered Fab

Randomized, double-masked
Included **foveal and non-foveal** lesions
Stratified for lesion location and lesion size
12 months (n=270)

- **Sham monthly or every other month** (n=89)
- **ANX007 5mg monthly (EM)** (n=89)
- **ANX007 5mg every other month (EOM)** (n=92)

PRIMARY BIOMARKER ENDPOINT

Change in GA lesion area as assessed by fundus autofluorescence at Month 12

PRESPECIFIED SECONDARY FUNCTIONAL ENDPOINTS

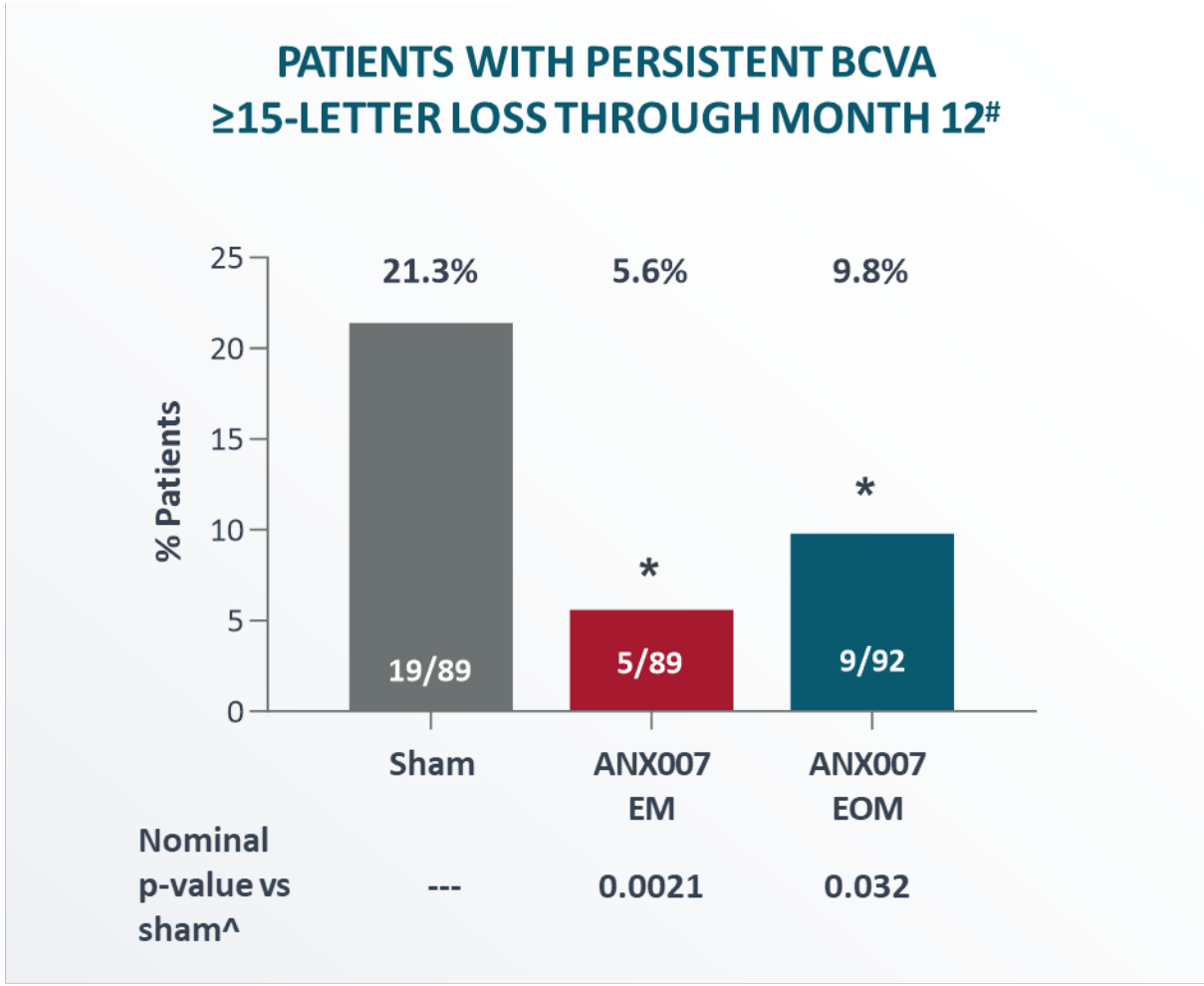
Best Corrected Visual Acuity (BCVA)
Low Luminance Visual Acuity (LLVA) & Deficit (LLVD)

Off-treatment
(6 months)

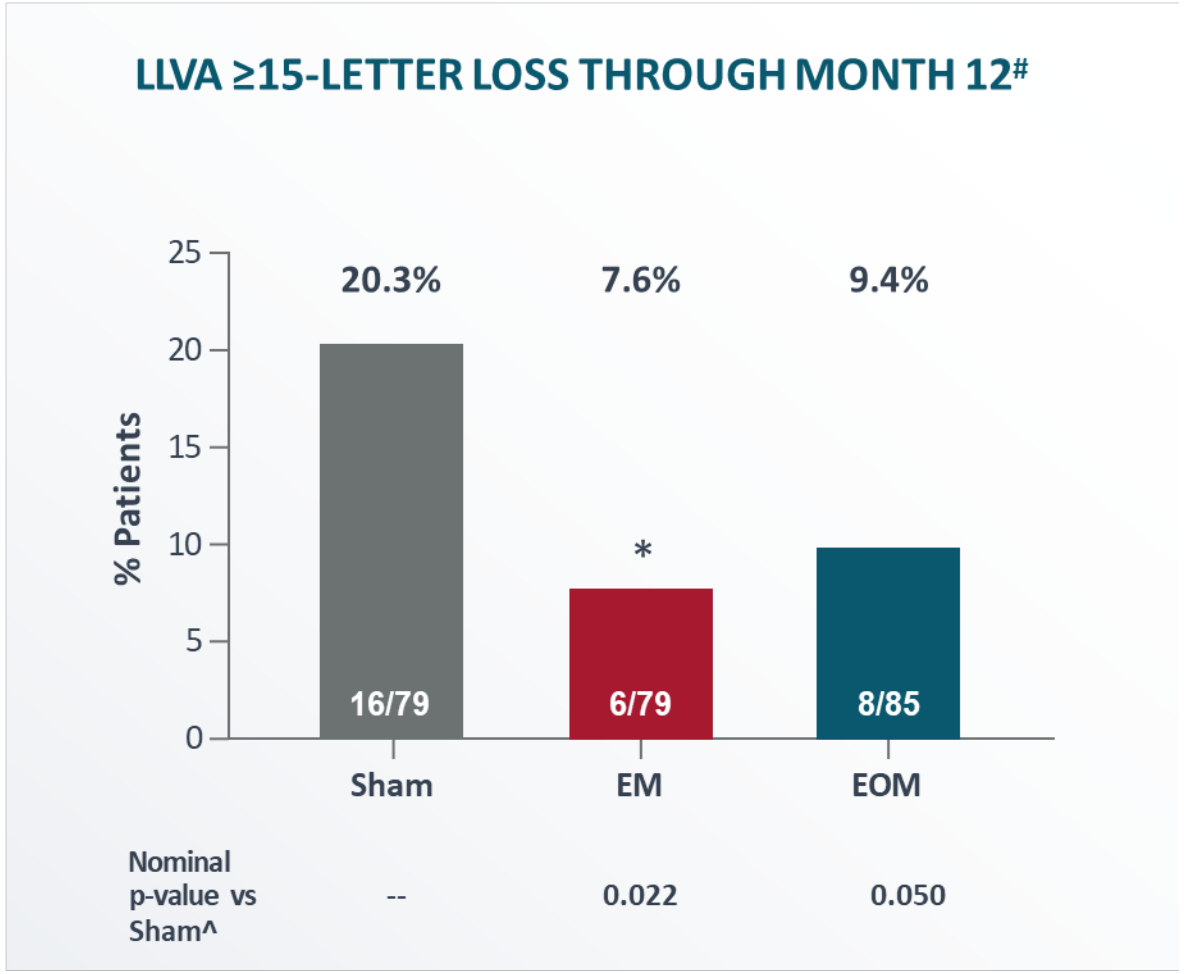
END OF STUDY
Month 18

Consistent, Significant Protection from Vision Loss: BCVA and LLVA

First demonstration of consistent, dose dependent preservation across multiple measures of visual acuity



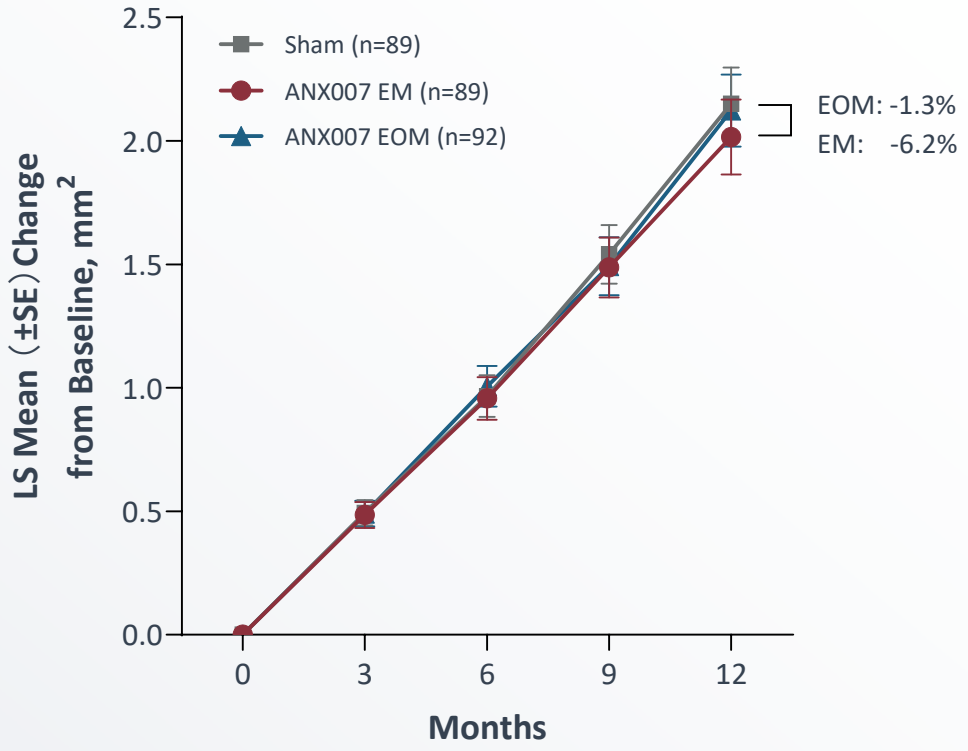
#Persistent for two consecutive visits through month 12 or at last study visit
^Nominal p-value from a Chi-square test in ITT population: * Nominal $p < 0.05$
Final data



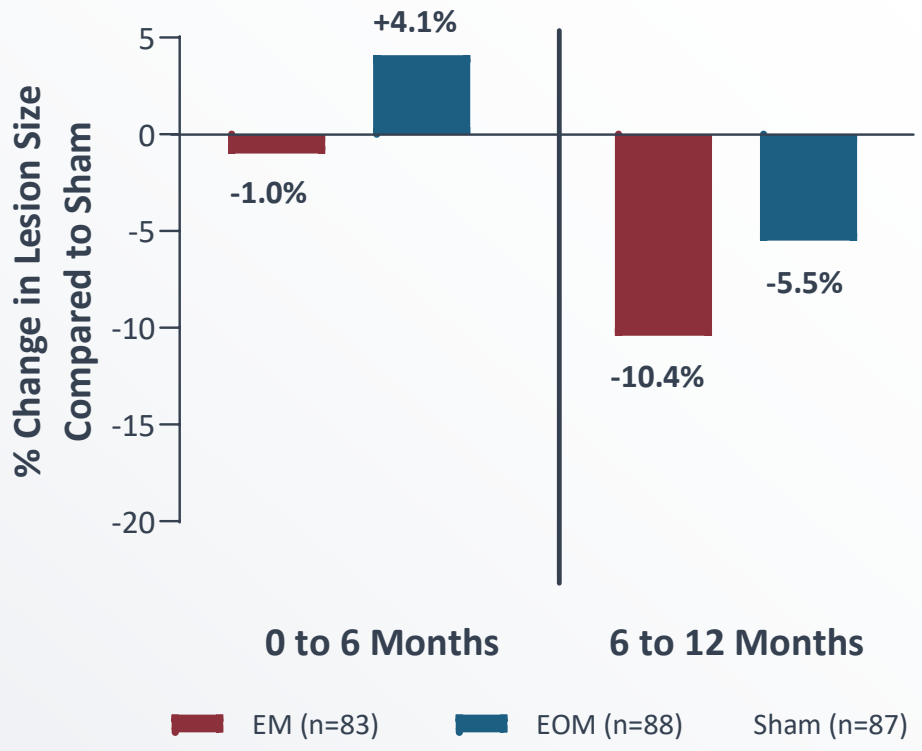
#Patients with single LLVA ≥15-letter loss event and at least one post-baseline LLVA measurement
^Nominal p-value from a Chi-square test
Final data

ANX007 Did Not Significantly Reduce RPE Biomarker Loss Across Full Retina, but Effects Increased Over Time

RPE LOSS FROM BASELINE TO MONTH 12#



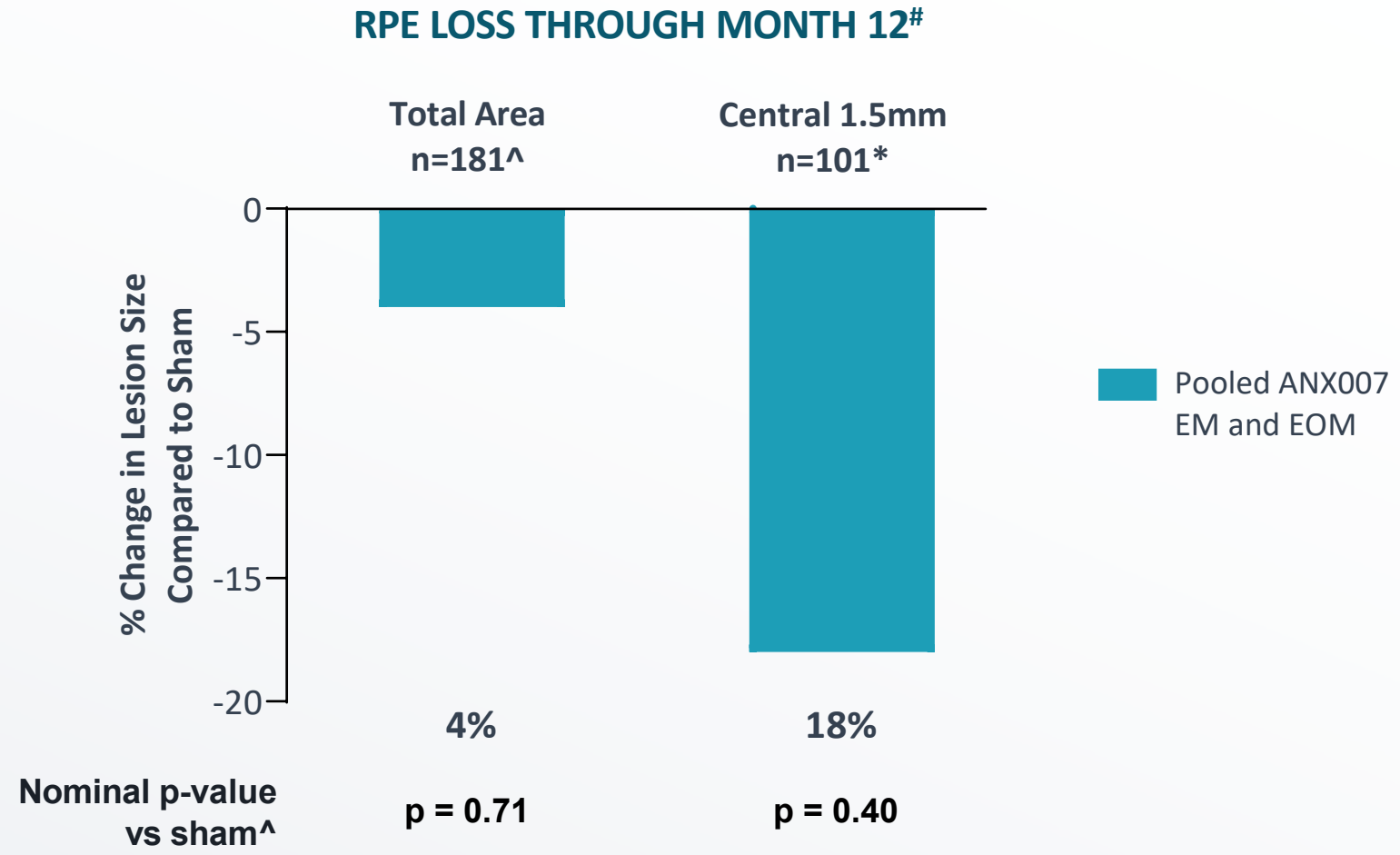
CHANGE IN RPE LOSS OVER TIME#



#Least-square (LS) mean and its standard error (SE) are based on a mixed-effect model for repeated measures (MMRM) adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.

ANX007 Protection from RPE Loss More Robust in 1.5 mm Foveal Center

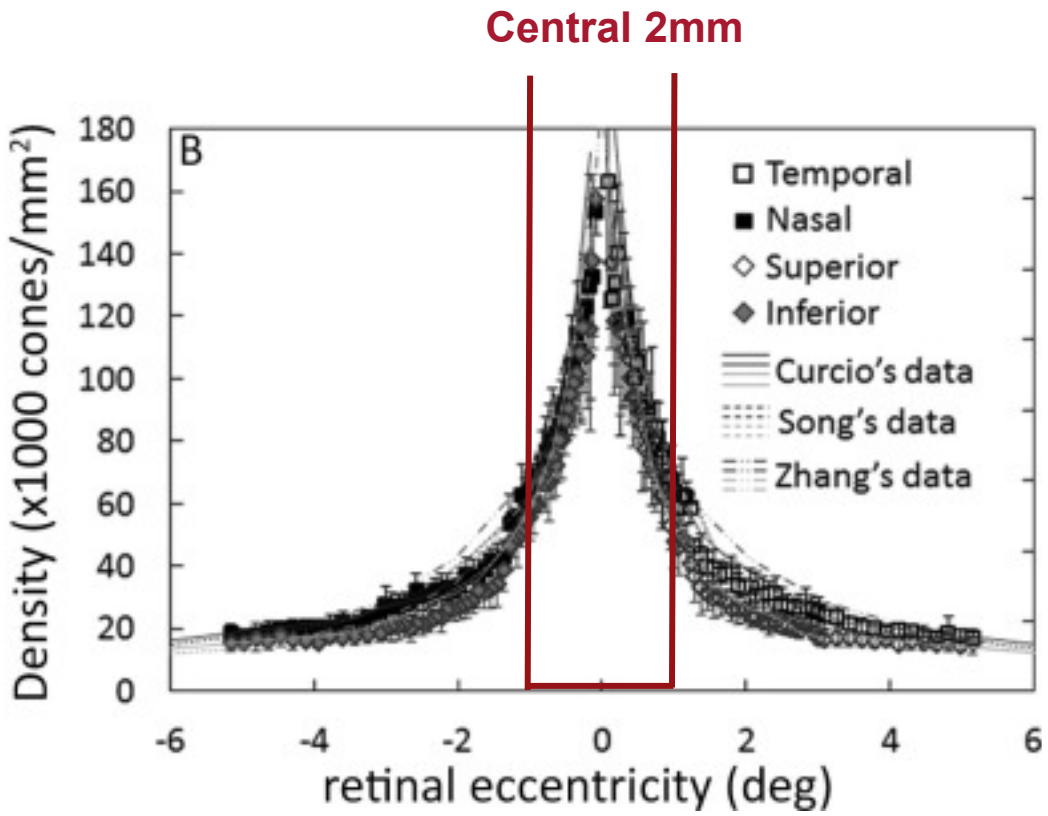
Consistent with treatment that protects from vision loss



#From a mixed model for repeated measures (MMRM) analysis; ^ITT population
*Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy at baseline

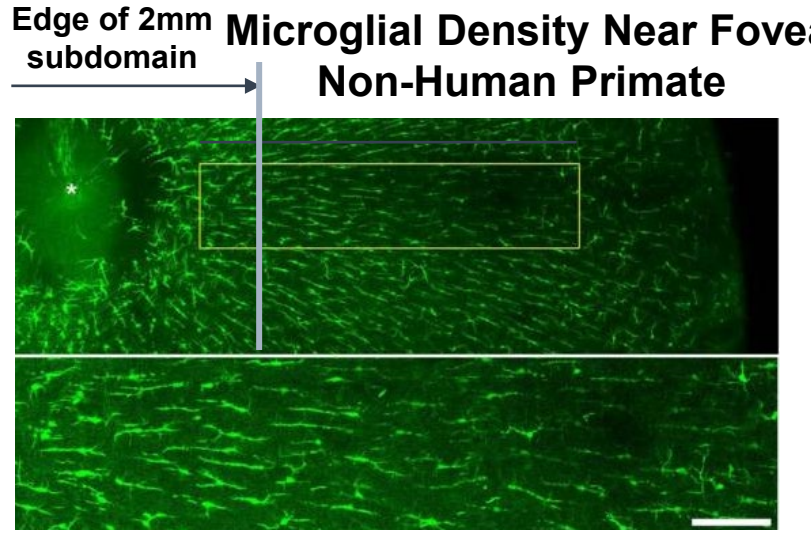
Cone and Microglia Densities Peak at the Fovea

Average Cone Density Across Retina Greatest With Central 2mm Subdomain



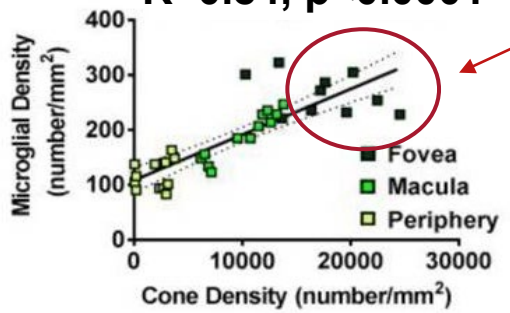
Sawides et al Vision Research, Volume 132, March 2017, Pg 34-44

Density of Microglia, C1q Effector Cell, Higher Near Central 2mm Subdomain



Correlation to Microglial Density in OPL

R=0.84, p<0.0001

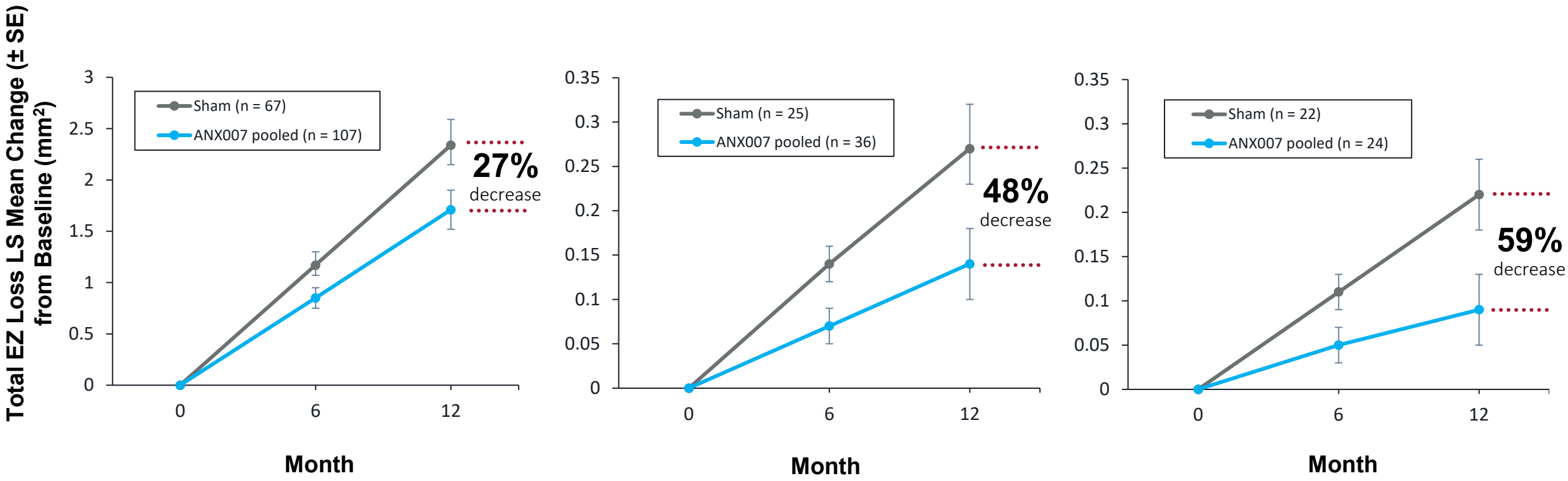


Increased cones density associated to increased microglia in OPL

Sinagravelu J, eta al. Brain Struct Funct. 2017

Significant Photoreceptor Protection Through 12 Months

More robust protection with ANX007 in central fovea, area best associated with vision, compared to pan-macula



Nominal p-value^		
	ANX007 Pooled vs Sham 0.0457	ANX007 Pooled vs Sham 0.0218	ANX007 Pooled vs Sham 0.0319

^Nominal p-values from a linear mixed model for repeated measures model (slope) analysis;
Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy/attenuation at baseline

ANX007: A Novel Neuroprotective Agent Demonstrating Consistent Vision Protection Now in Phase 3

Blocking C1q for neuroprotection, prevented synapse loss and protected photoreceptors from elimination in animal models

ANX007 consistently protected against the loss of visual acuity in ARCHER Phase 2 study

ANX007 protected central retinal structures closely associated with visual function

ANX007 was generally well-tolerated with strong benefit / risk profile

Global Phase 3 program NOW ONGOING