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Neuroinflammation, Neurodegeneration, and New Perspectives in Dry AMD with GA

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Neuroinflammation: A Key Driver of Neurodegeneration in Dry AMD with GA

- C1q is a common driver of neuroinflammation and neurodegeneration in the central and peripheral nervous systems
- Inhibition of C1q represents a unique neuroprotective mechanism

Targeting C1q-Mediated Neurodegeneration – Preservation of Synapses & Neuronal Function

Dr. Ben Barres discovery of C1q's role in neurodegeneration (2007) › **Spawned entire fields and Validated in labs world-wide[1]** › **Anti-C1q protective in several disease models**

Ben Barres, M.D., Ph.D.
Discoverer of C1q Technology
Chair of Neurobiology at Stanford University
Scientific Co-Founder, Annexon

KEY DISCOVERIES:

1. C1q normally functions to eliminate excess synapses in development[1]
2. C1q-mediated synaptic pruning is common pathway of neurodegeneration
3. C1q inhibition protects against synapse loss and neurodegeneration in several disease models[2]

- Alzheimer's disease
- Amyotrophic Lateral Sclerosis
- Frontotemporal dementia
- Geographic Atrophy
- Glaucoma
- Guillain-Barré Syndrome
- Huntington's disease
- Retinal ischemia
- Schizophrenia
- Spinal muscular atrophy
- Traumatic brain injury

[1]Stevens, et al., 2007 DOI 10.1016/j.cell.2007.10.036; Schafer et al., 2012 DOI 10.1016/j.neuron.2012.03.026; Hong, et al., 2016 doi: 10.1126/science.aad8373; Lui et al., 2016 doi.org/10.1016/j.cell.2016.04.001; [2]Yednock, et al, 2022, doi.org/10.1186/s40942-022-00431-y

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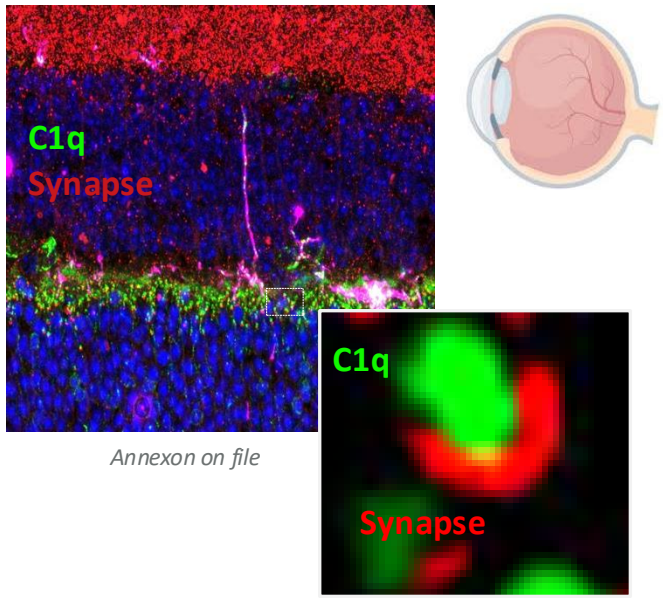
C1q is a Common Driver of Neurodegeneration in Both the Central (CNS) and Peripheral Nervous System (PNS)

C1q directly binds to synapses on stressed neurons, triggering elimination

C1q targeting synapses for elimination in the retina[1]

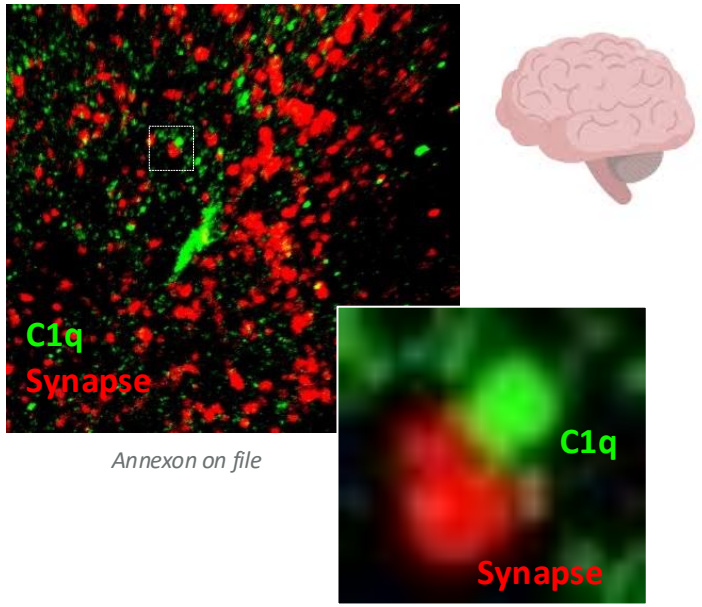
MODEL OF PHOTORECEPTOR DEGENERATION



Annexon on file

C1q targeting synapses for elimination in the brain[2]

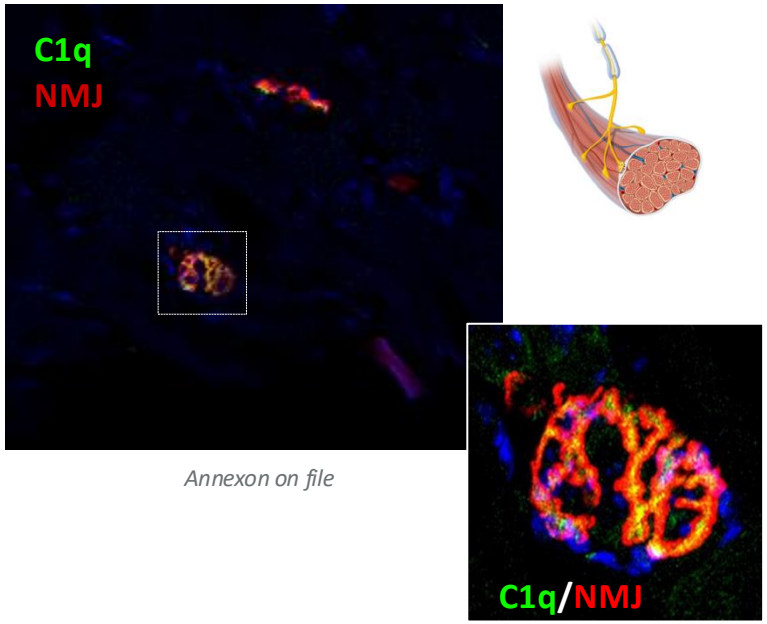
MODEL OF HUNTINGTON'S DISEASE



Annexon on file

C1q targeting neuromuscular junction (NMJ) for elimination in the PNS[3]

MODEL OF AMYOTROPHIC LATERAL SCLEROSIS



Annexon on file

C1Q INHIBITION PROTECTS AGAINST SYNAPSE LOSS AND NEURODEGENERATION IN SEVERAL DISEASE MODELS[4]

[1]Stevens, et al., 2007 DOI 10.1016/j.cell.2007.10.036; [2]Wilton, et al., 2023, doi: 10.1038/s41591-023-02566-3; [3]Idriss, et al., 2016 doi: 10.1186/s12974-016-0538-2
[4]Yednock, et al, 2022, doi.org/10.1186/s40942-022-00431-y

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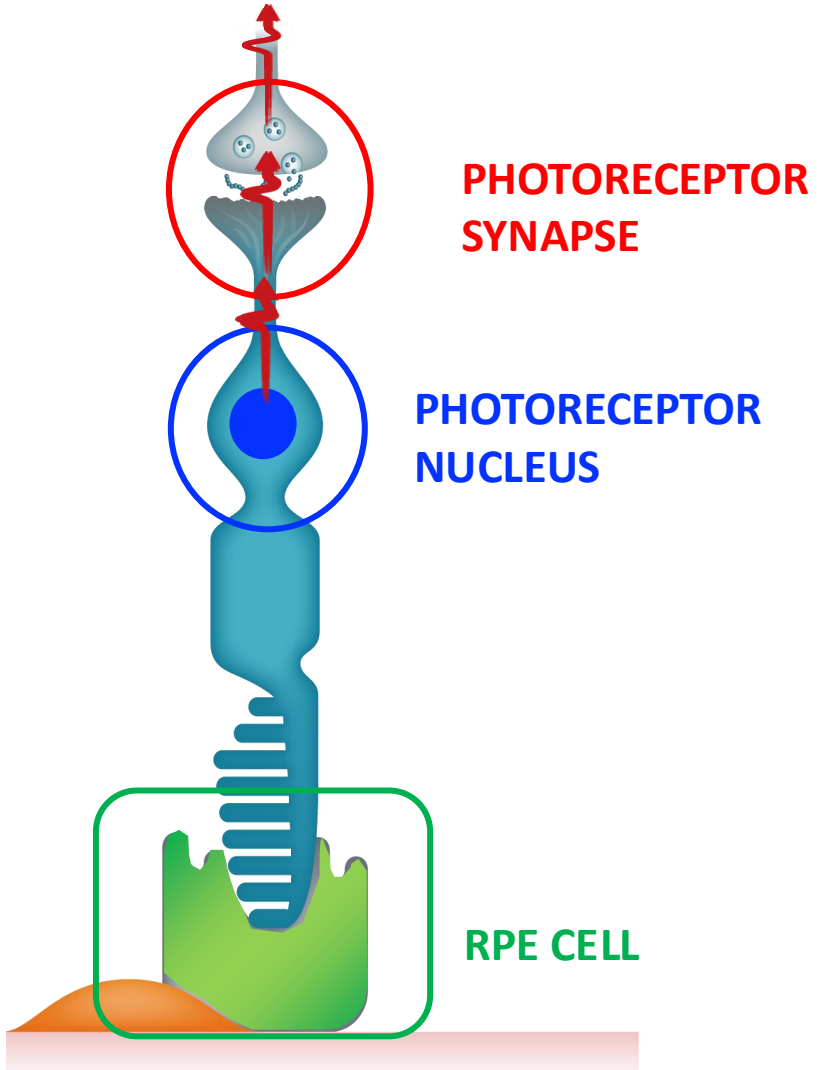
Synapses are vital to neuronal function and survival



[1]Davies et al., 1987 J Neurological Sci 78:151; Terry, et al., 1991 Ann Neurol 30:572: [2]Tassoni, et al., SFN 2022; Annexon data on file; Jiao, et al., 2018 *Mol Neurodegener* **13**:45; Katschke, 2018 Sci Rep. **8**:7348. [3]Lansita, et al., 2017 *International Journal of Toxicology*, **36**:449; [4]Yednock, et al., 2022 *Int J Retina Vitreous* **8**:79

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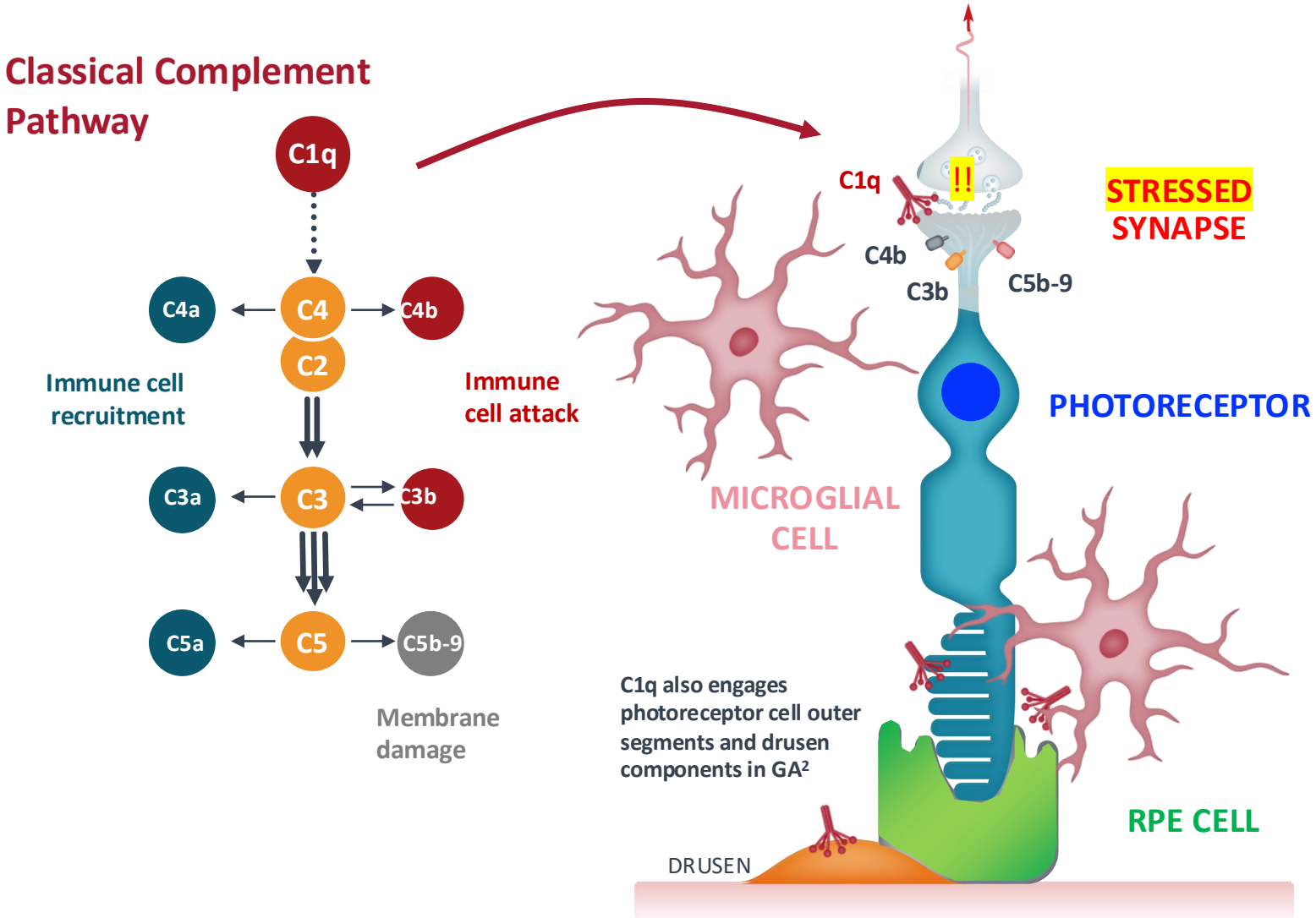
C1q-Mediated Neurodegeneration: It Starts at the Synapse

C1q drives synapse loss, neuron loss, and neuroinflammation in multiple neurodegenerative diseases[1]



- **C1q recognizes synapses on stressed neurons in diseased state and tags them for removal**
- **This process anchors activation of the classical pathway on the synapse surface**
- **Microglial cells attack and remove complement-coated synapses**
- **Synapse elimination results in neuronal cell death and visual function loss**
- **C1q and neuroinflammation become key parts of the neurodegenerative process**

[1]Stevens, 2007, *Cell* **131**:1164; Howell, 2011 *J Clin Invest*. **121**:1429; Schafer, 2012 *Neuron* **74**: 691; Hong, 2016 *Science*. **352**:712; Dejanovic, 2018 *Neuron* **100**:1322; Yoshiyama, 2007, *Neuron* **53**:337; Lui, 2016 *Cell* **165**:921; Vukojicic, 2019, *Cell Rep* **29**:3087; Williams, 2016 *Mol Neurodeg* **11**:26; Tassoni, SFN 2022 Annexon data on file; Jiao, 2018 *Mol Neurodeg* **13**:45; Katschke, 2018 Sci Rep. **8**:7348; [2]Katschke, 2018 *Sci Rep* **8**:7348; Yednock, 2022 *Int J Ret Vit* **8**:79

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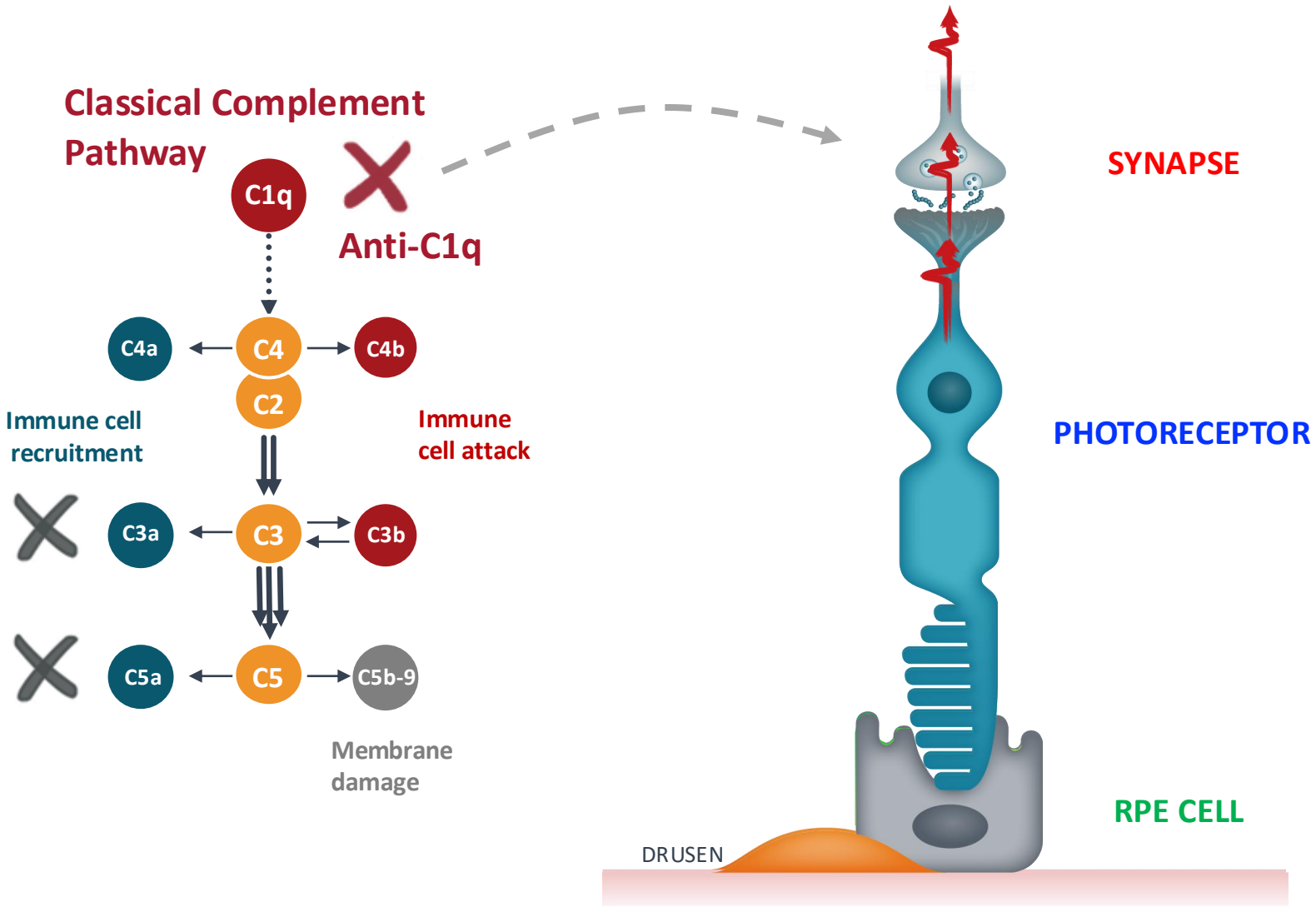
Anti-C1q: A Distinct Neuroprotective Mechanism



Blocking C1q:

- Stops the entire classical cascade and all downstream activity[1]
- Protects synapses from elimination
- Leaves lectin and alternative complement pathways in place to perform normal clearance and immune functions

Blocking C3 or C5:

- Does not stop upstream component deposition
- Build-up of upstream deposition can allow cascade bypass[2]
- Blocks downstream activity of lectin and alternative complement pathways

[3]Lansita, et al., 2017 *Intl J Tox*, **36**:449 (DOI: 10.1177/1091581817740873); [2]Mannes, et al., 2021 *Blood* **137**: 443 (doi: 10.1182/blood.2020005959)

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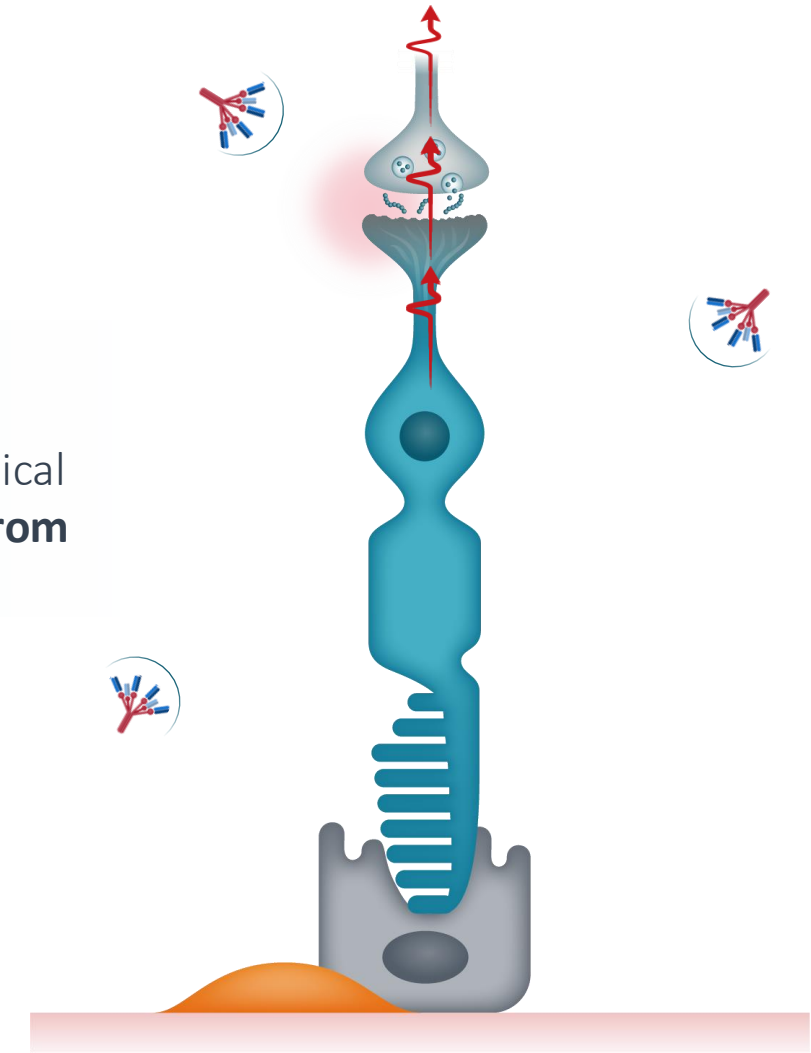
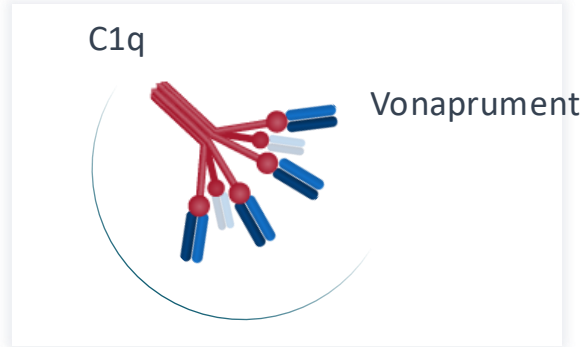
Vonaprument (ANX007) Inhibits C1q

C1q drives photoreceptor synapse & cell loss and neuroinflammation

Vonaprument inhibits C1q and all damaging components of the classical pathway[3] and **protects synapses from elimination**





[1]Davies et al., 1987 J Neurological Sci 78:151; Terry, et al., 1991 Ann Neurol 30:572: [2]Tassoni, et al., SFN 2022; Annexon data on file; Jiao, et al., 2018 *Mol Neurodegener* **13**:45; Katschke, 2018 Sci Rep. **8**:7348. [3]Lansita, et al., 2017 *International Journal of Toxicology*, **36**:449; [4]Yednock, et al., 2022 *Int J Retina Vitreous* **8**:79

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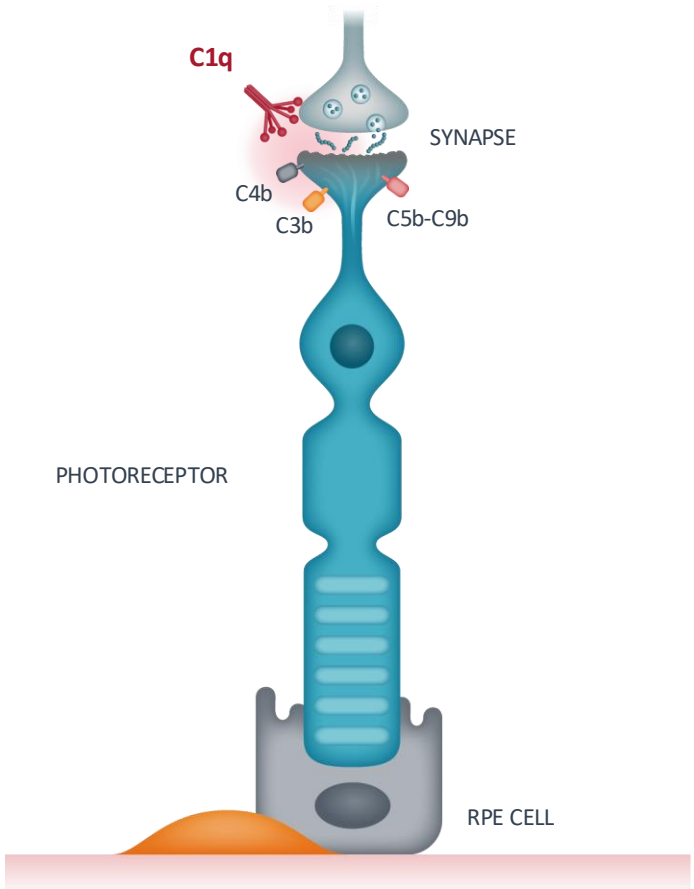
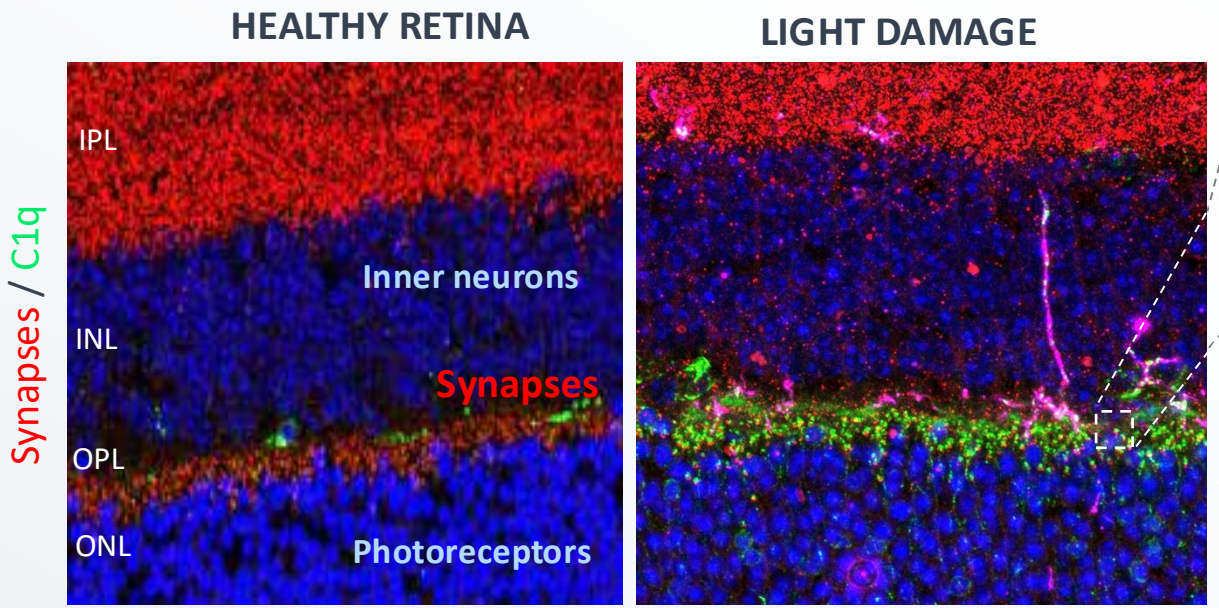
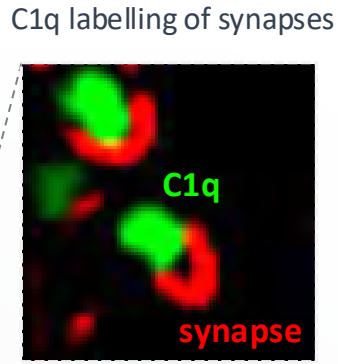
C1q Recognizes and Eliminates Photoreceptor Synapses in a Model of Photoreceptor Degeneration

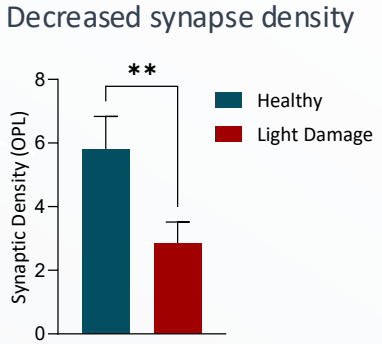
C1q binds stressed photoreceptor synapses



C1Q SELECTIVELY RECOGNIZES SYNAPSES ON DAMAGED PHOTORECEPTOR NEURONS IN A MODEL OF LIGHT-INDUCED DAMAGE







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

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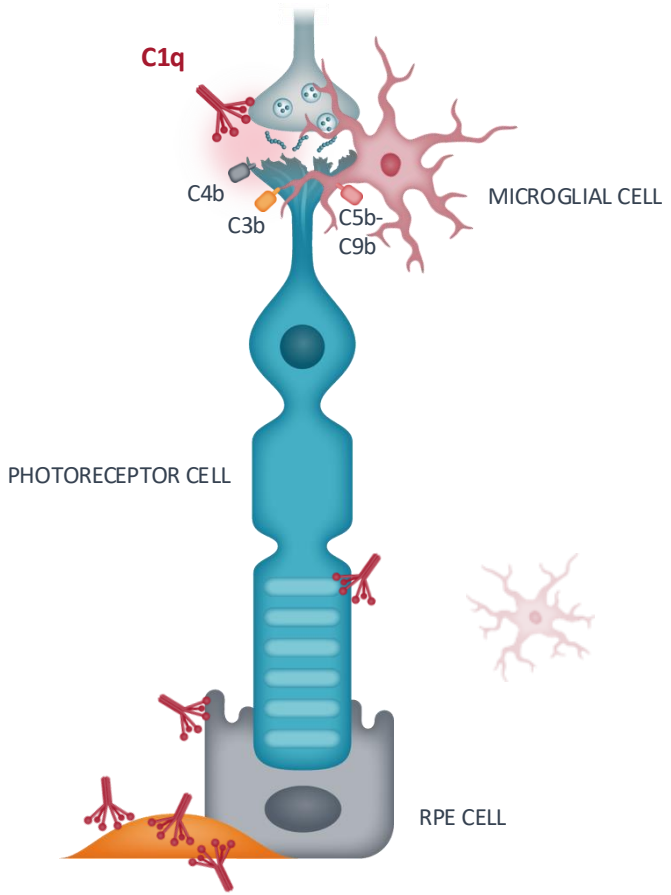
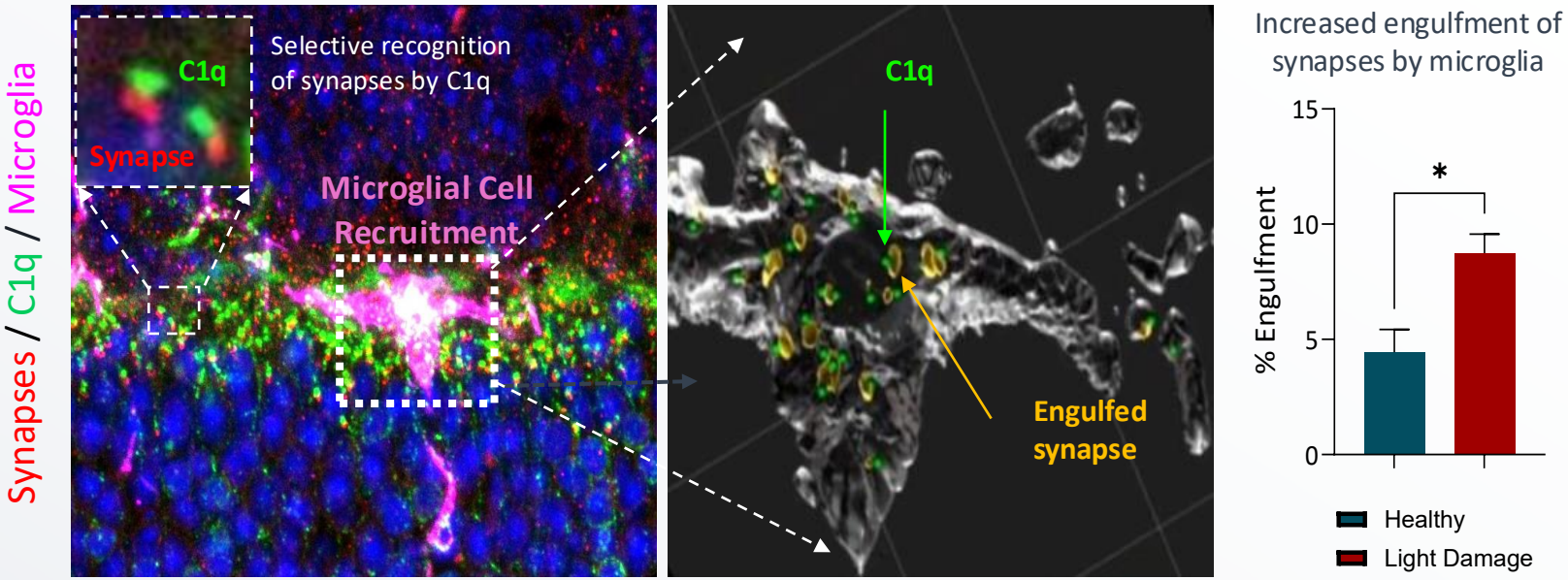
C1q Drives Synapse Destruction and Removal by Microglia in a Model of Photoreceptor Degeneration

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



MICROGLIAL ENGULFMENT OF C1Q-COATED SYNAPSES



Representative IF images showing staining for photoreceptor synapses (BSN, red), C1q (green) and microglia (Iba1, magenta) in retina section from light damaged animals at Day 3. Increased C1q Tagging of photoreceptor synapses of the OPL is shown in inset (i). Nuclei counterstained with DAPI (Blue). Inset (ii) is depicting a microglia cell residing over the OPL layer and engulfing C1q tagged synaptic material, as shown in the high resolution and 3D surface rendered image. Nuclei counterstained with DAPI (Blue). Quantification of % engulfment by microglia of photoreceptor synaptic puncta of the OPL, confirming increased engulfment in light damaged retina at Day 3 compared to naïve (n=3 per group, Student T test, *P<0.05. **P<0.01.

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

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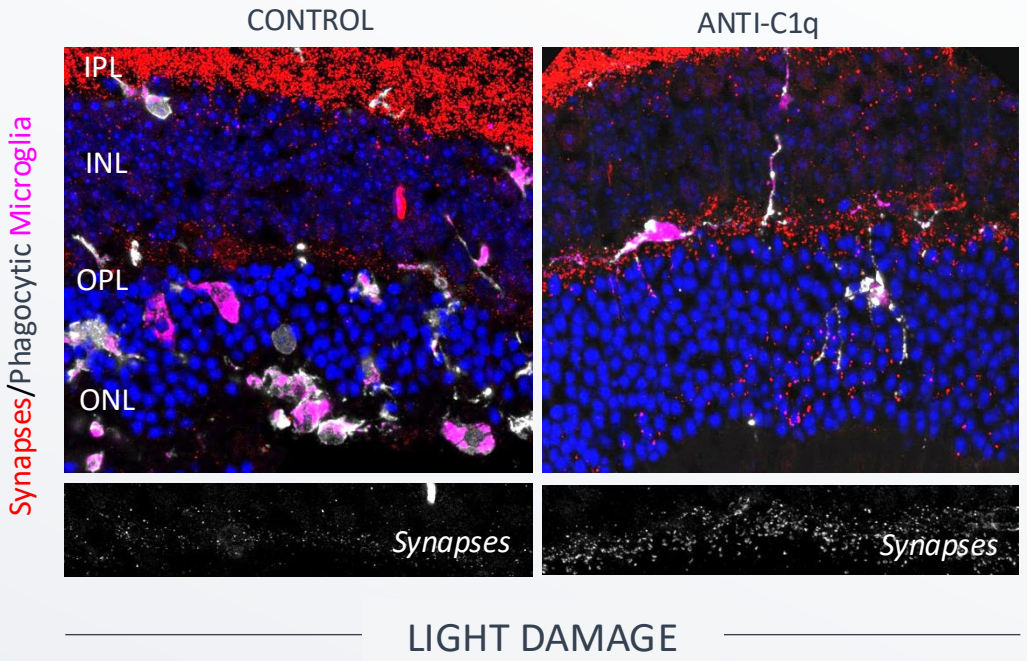
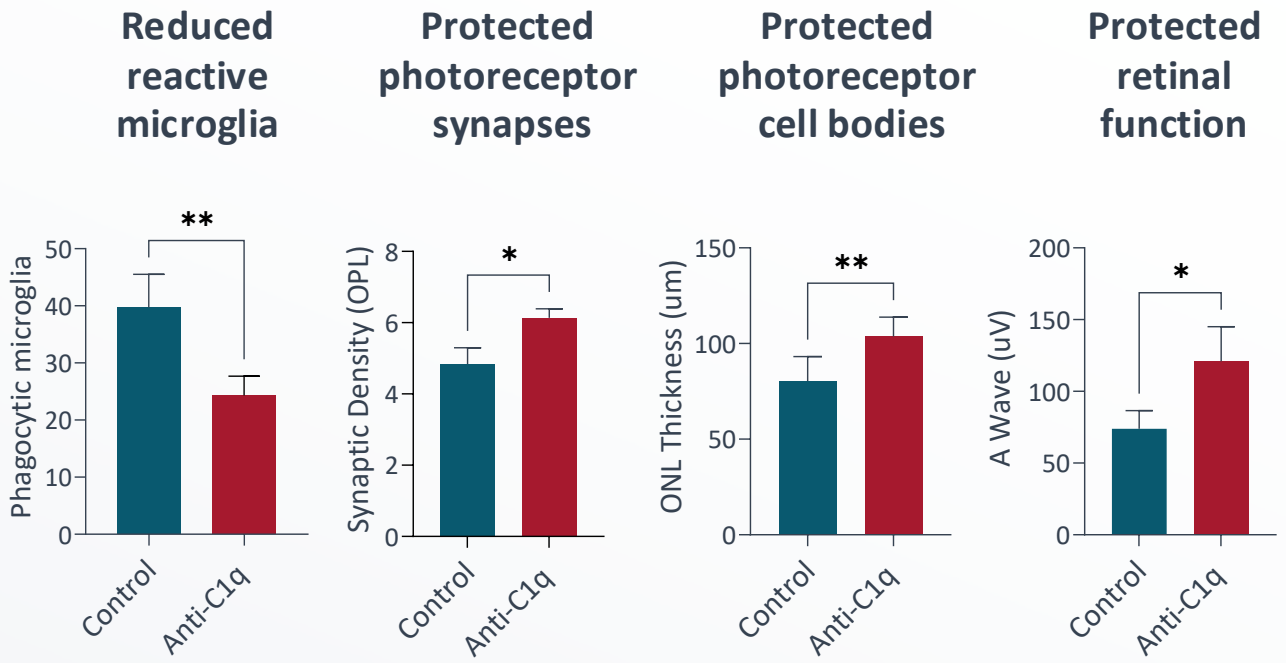
Anti-C1q Protected Photoreceptor Cells and Function in Models of Photoreceptor Damage

ANTI-C1Q TREATMENT REDUCED INFLAMMATION AND **PRESERVED PHOTORECEPTOR SYNAPSES AND CELL BODIES**





*p < 0.05
**p < 0.01

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

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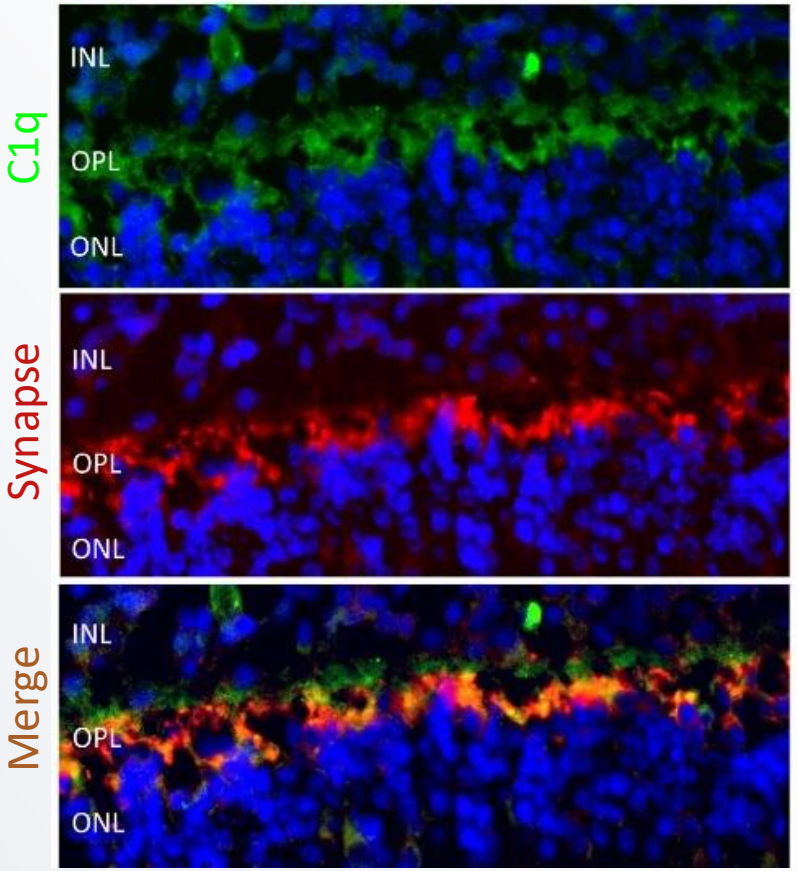
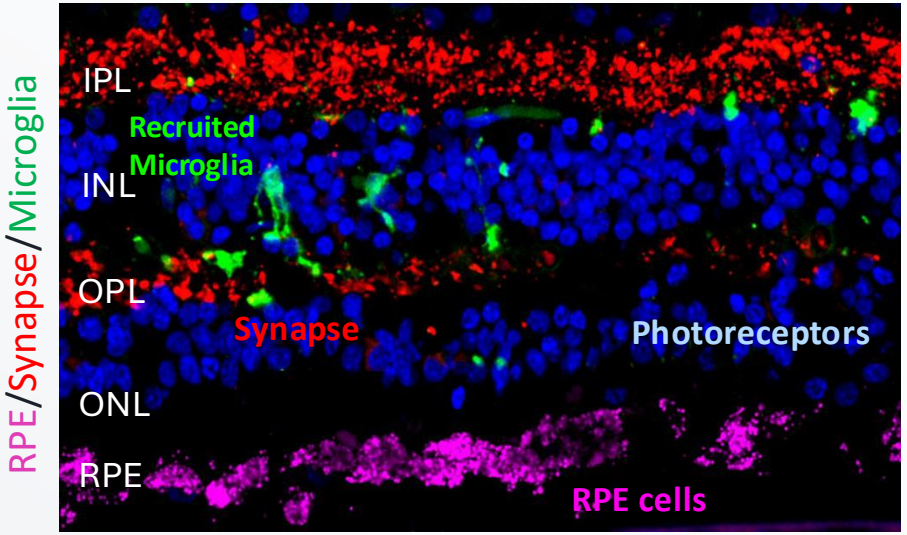
Evidence of C1q in Human GA: C1q Deposition on Photoreceptor Synapses and Microglia Recruitment in Postmortem GA Retinal Tissue

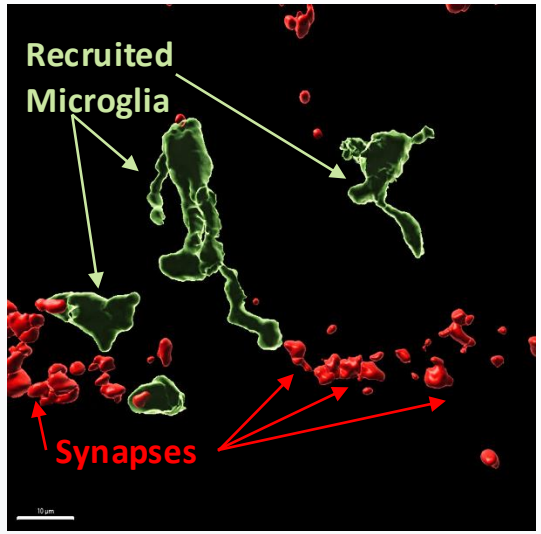
C1Q DEPOSITION ON PHOTORECEPTOR SYNAPSES



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;

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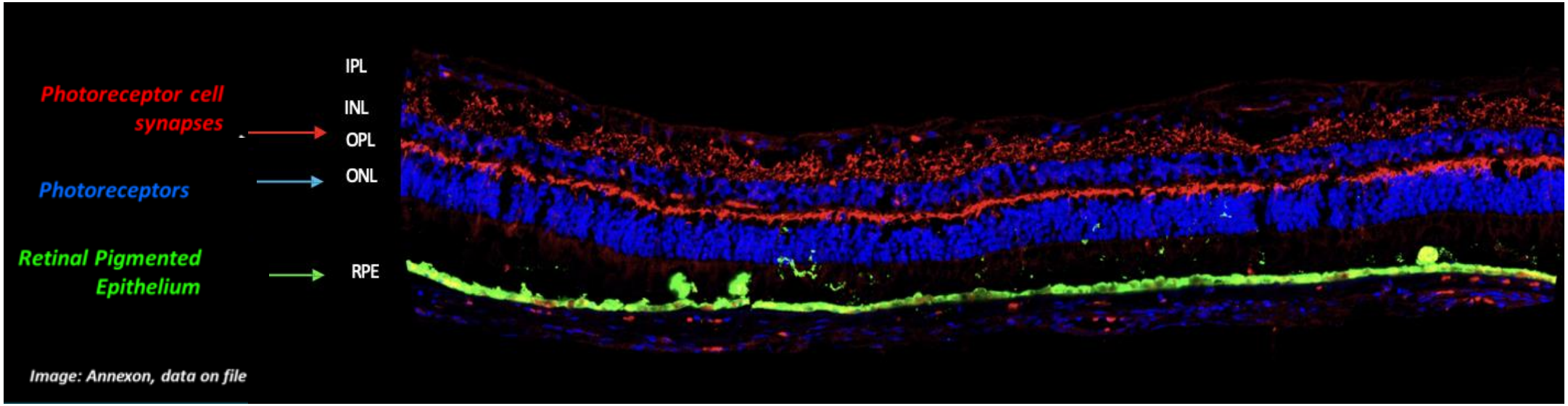
Healthy Human Retina Tissue Section

Uniform layers of photoreceptors and synapses



[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

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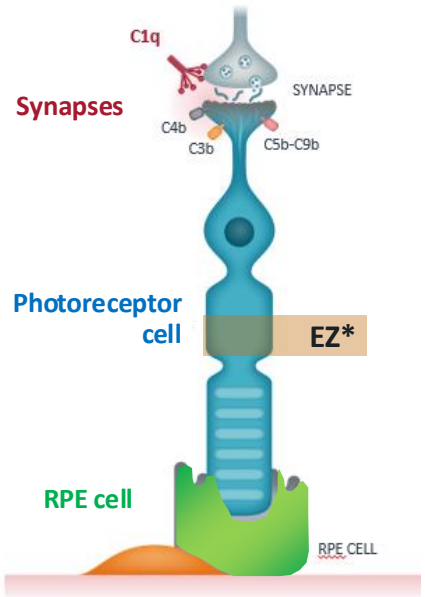
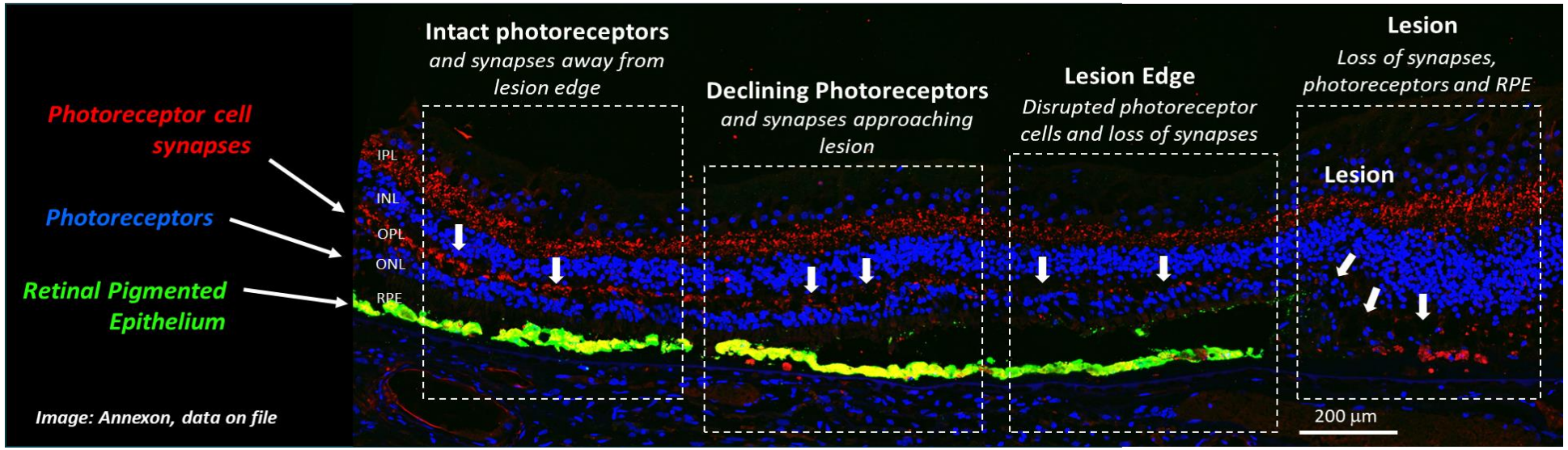
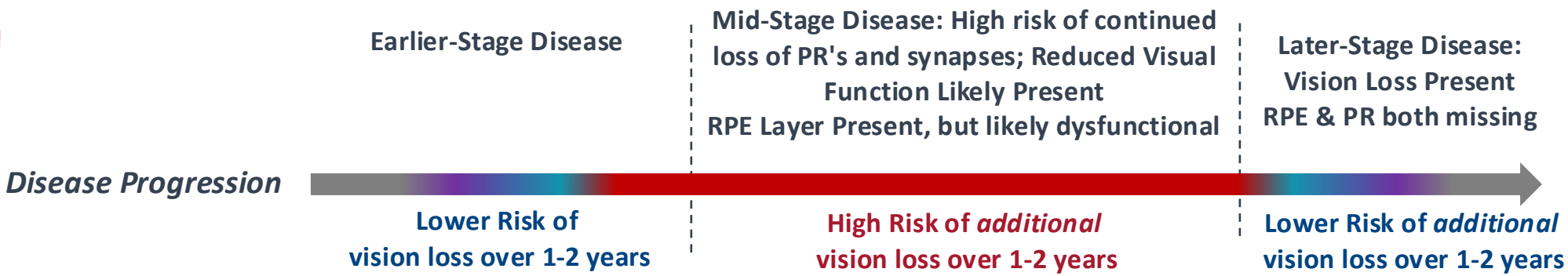
Retina with Geographic Atrophy: Human Tissue Section

- **Photoreceptors and RPE Cells provide bidirectional trophic support to each other**
- **In dry AMD with GA, the area of EZ loss is larger than the area of RPE loss; RPE loss occurs after EZ loss**
- **Blocking C1q with Vonaprument: Protects vulnerable synapses on stressed photoreceptors, thereby protecting vision**



*The EZ represents the outer portion of PR inner segments where mitochondria are densely concentrated, creating a visible imaging layer on OCT





Section Wrap-Up

- **C1q-mediated synapse and neuron elimination is a common pathway in neurodegenerative disease in the central and peripheral nervous system**

- **Dry AMD with GA** is a neurodegenerative disease, with **progressive vision loss resulting from C1q-mediated elimination of photoreceptor synapses**, and ultimately photoreceptors and then RPE
  - Co-localization of C1q and photoreceptor synapses, and microglial engulfment of synapses, is common to both animal models and human retinal GA lesions

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- **Inhibition of C1q** in animal models of photoreceptor damage **protects from synaptic loss**, and ultimately protects photoreceptors and their function

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- **In human GA lesions, the loss of photoreceptors and synapses precedes RPE loss**
  - Assessing disease progression using functional parameters, such as visual acuity, is critical to determining therapeutic effect, as opposed to RPE lesion area alone

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The Phase 2 ARCHER Study: Key Efficacy and Safety Outcomes

- Fewer vonaprument-treated eyes experienced clinically meaningful vision loss compared to sham
- No increased incidence of CNV; no cases of ischemic optic neuropathy or retinal occlusive vasculitis

ARCHER: Phase 2 Trial Of The C1q Inhibitor Vonaprument (ANX007) in Patients with Dry AMD and GA

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

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

PRIMARY ENDPOINT

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

PRESPECIFIED FUNCTIONAL ANALYSES

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

Off-treatment
(6 months)

END OF STUDY
Month 18

Patient Demographics and Study Eye Baseline Characteristics Generally Well-Balanced Across Groups

CHARACTERISTIC	SHAM POOLED (N=89)	VONAPRUMENT EM (N=89)	VONAPRUMENT EOM (N=92)
Age, mean (SD)	79.8 (7.49)	79.7 (8.64)	80.5 (8.53)
Female, n (%)	59 (66.3%)	47 (52.8%)	60 (65.2%)
Caucasian, n (%)	86 (96.6%)	88 (98.9%)	89 (96.7%)
Mean BCVA, mean (SD)	**58.5 (16.2) ~20/70**	**58.8 (17.2) ~20/70**	**57.9 (15.3) ~20/70**
Foveal Lesion	49.4%	57.3%	53.3%
GA Lesion Size (mm^2), mean (SD)	7.28 (3.99)	7.28 (3.96)	7.53 (4.10)
GA Lesion < 7.5 mm^2	61.8%	58.4%	57.6%
Fellow Eye CNV	22.5%	24.7%	17.4%
Multifocality, n (%)	65 (73.0%)	61 (68.5%)	67 (72.8%)

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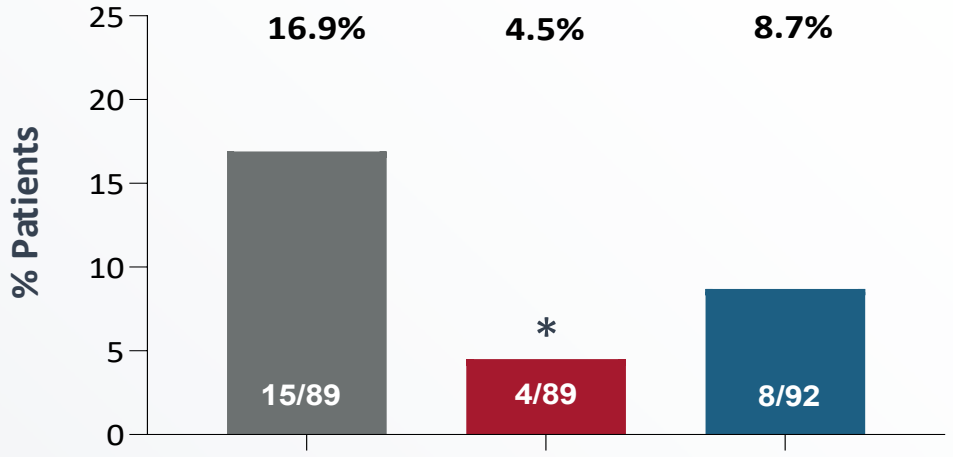
Fewer Vonaprument-Treated Eyes Experienced BCVA ≥15-Letter Loss Compared to Sham

PROPORTION OF PATIENTS WITH CONFIRMED BCVA ≥15-LETTER LOSS AT TWO CONSECUTIVE VISITS THROUGH MONTH 12*



Nominal p-value vs Pooled Sham^	---	Vonaprument EM 0.0076	Vonaprument EOM 0.0994

*BCVA ≥15-Letter Loss at Month 12 was confirmed at the subsequent visit (Month 15). In ARCHER, visits were monthly through Month 12 and then at Months 15 & 18

^Nominal p-value from a Chi-square test in ITT population: *Nominal p < 0.05

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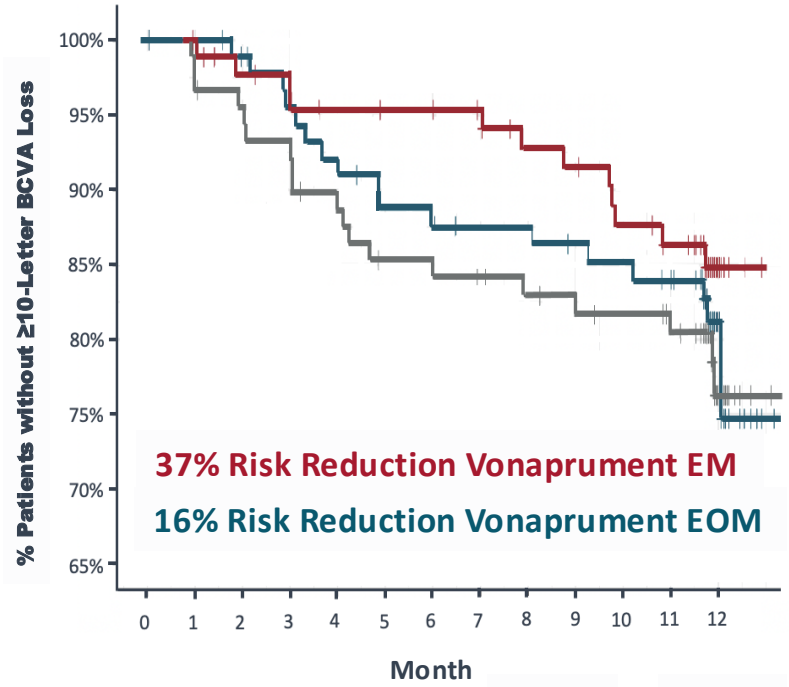
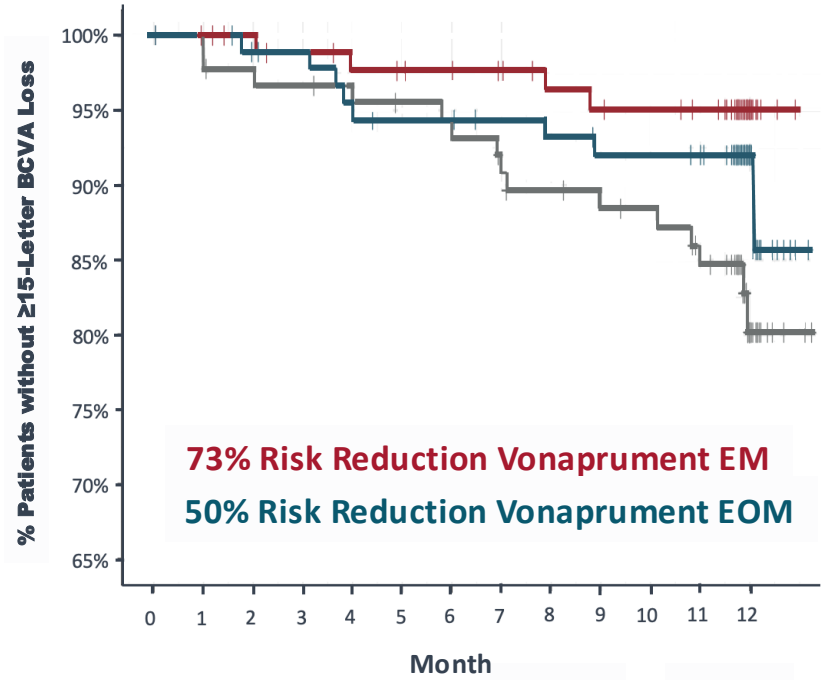
Visual Acuity Outcomes: BCVA ≥10-, ≥15- and ≥20-Letter Loss Through 12 Months

Persistent BCVA Vision Loss Through Month 12, Confirmed at Month 15

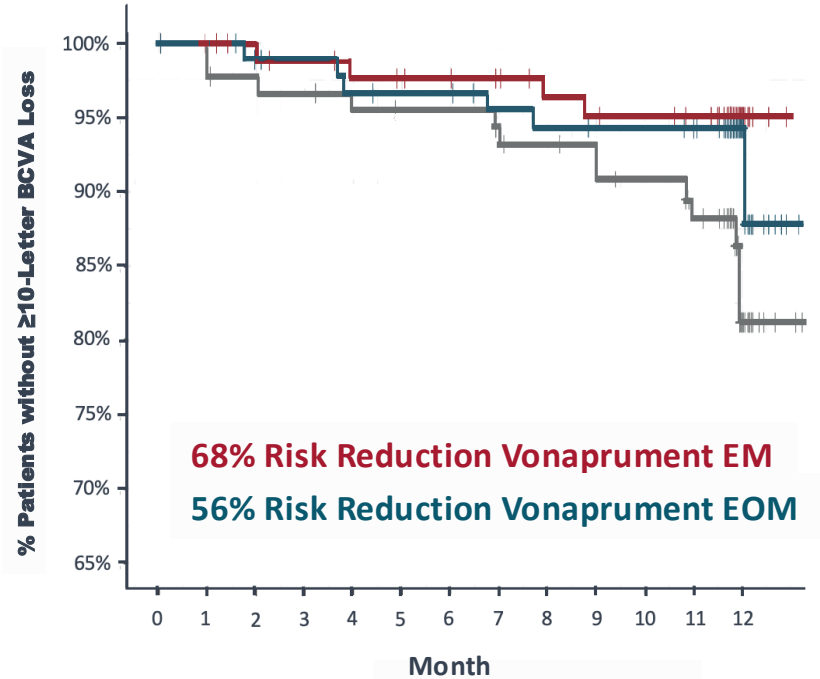
≥10-LETTER LOSS



≥15-LETTER LOSS



≥20-LETTER LOSS



Nominal p-value vs sham^	EM	EOM
≥10-LETTER LOSS	0.1952	0.6015
≥15-LETTER LOSS	0.0119*	0.1098
≥20-LETTER LOSS	0.0330*	0.0841

#Persistent for two consecutive visits through month 12; month 12 confirmed at month 15 visit
^Nominal p-value from a Chi-square test in ITT population
* P < 0.05

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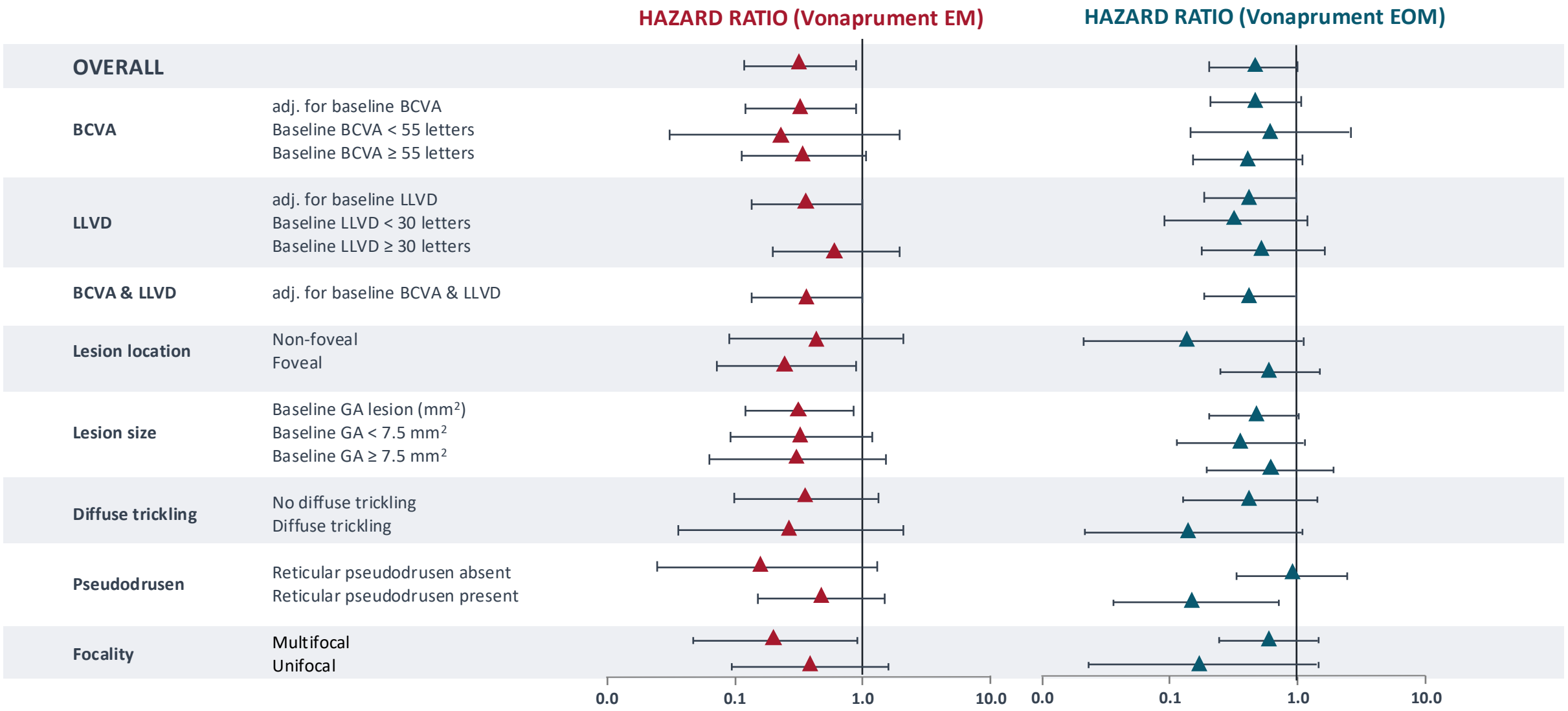
Hazard Ratio for ≥15 Letter Loss Was Consistent Across Baseline Characteristics



*persistent for two consecutive visits through month 12 or at last visit; Hazard ratios are from Cox regressions accounting for event time and censorship
NOTE: Hazard ratio not estimated for ANX007 EM vs Sham with baseline LLVD < 30 due to zero (0) event in Vonaprument EM group for the subgroup.

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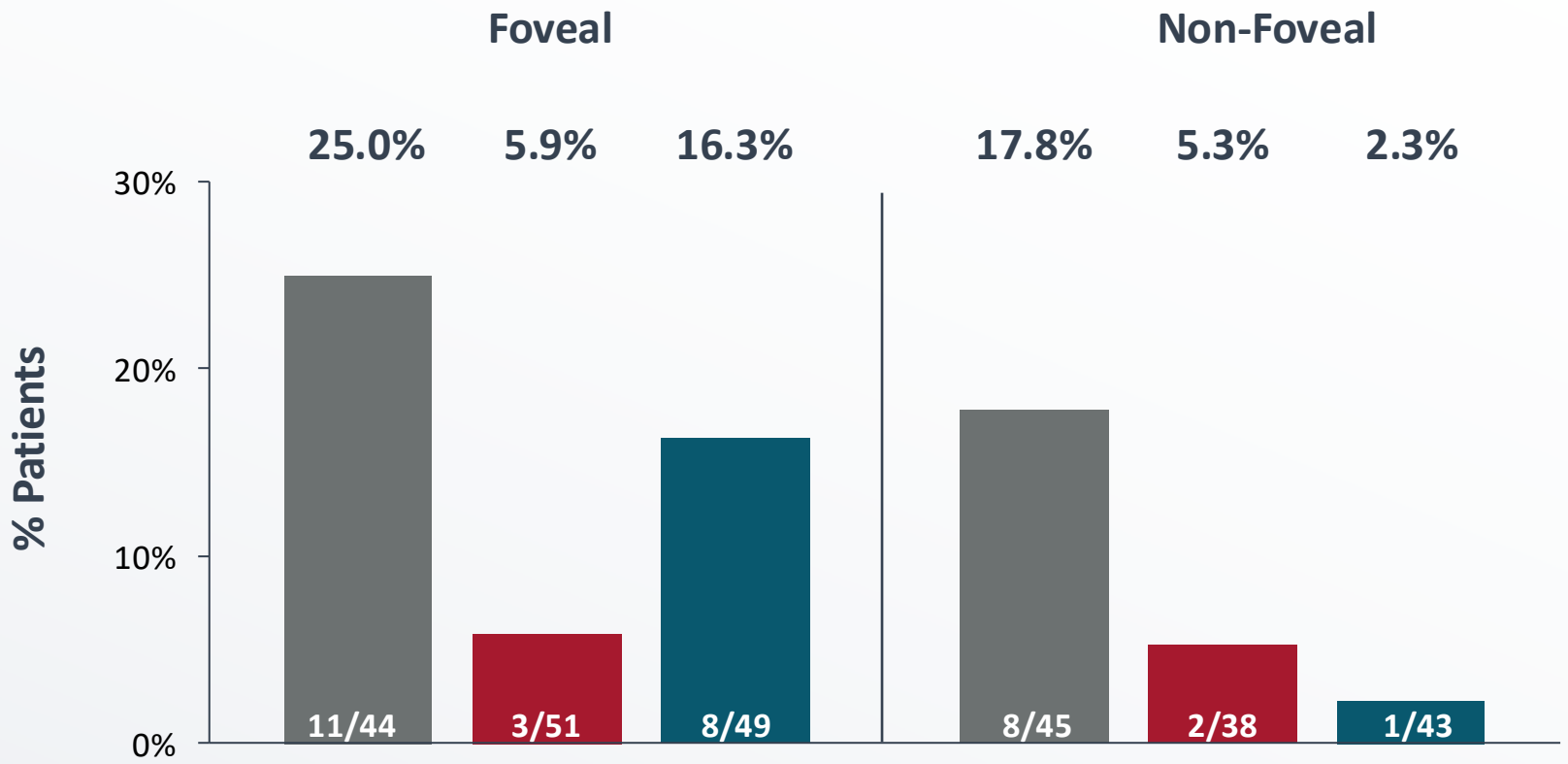
Subgroup Analysis: Visual Acuity Outcomes in Subfoveal and Non-Subfoveal Lesions

PATIENTS WITH CONFIRMED BCVA ≥15-LETTER LOSS THROUGH MONTH 12#



Nominal summary p- value vs. Pooled Sham^

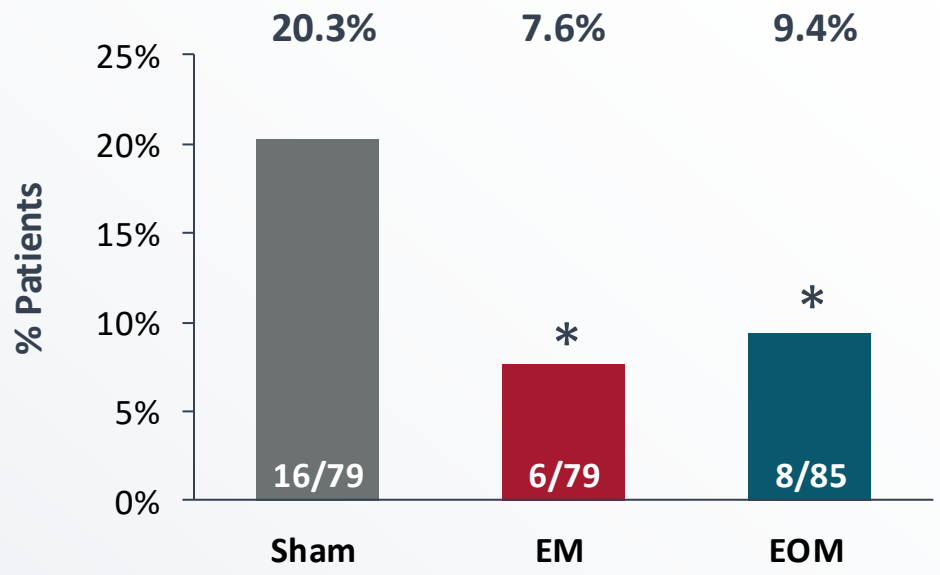
Vonaprument EM (pooled)	0.0019
Vonaprument EOM (pooled)	0.0254

#Confirmed two consecutive visits at any time through month 12 or at last study visit
^Nominal p-value from a Cochran Mantel-Haenszel test (General Association) in ITT population
Final data

Low Luminance Visual Acuity (LLVA) Outcomes Through Month 12

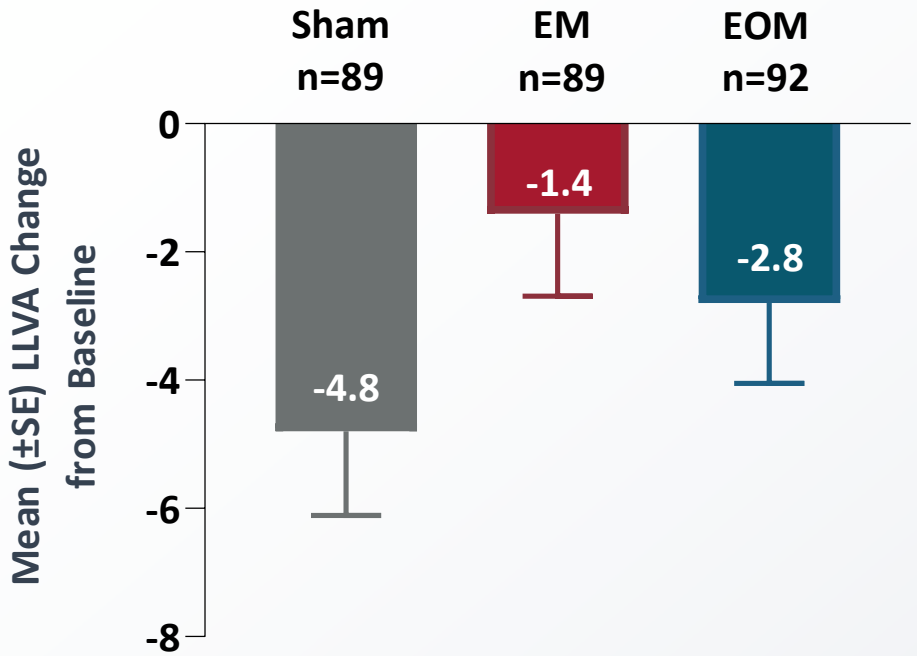
LLVA: Visual Acuity assessed under Low Luminance Conditions using a neutral density filter

LLVA ≥15-LETTER LOSS THROUGH MONTH 12#



Nominal p-value vs sham^	--	0.0216	0.0497

MEAN CHANGE FROM BASELINE IN LLVA AT MONTH 12+



Nominal p-value vs sham^	---	0.0592	0.2664

+Patients with at least one post-baseline LLVA measurement and two consecutive or last visit 15-letter loss events
^Nominal p-value from a Chi Square test; *p<0.05
Final data

+Mean, standard error (SE), and p-value based on MMRM adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.
^Nominal p-value from a Chi-square test in ITT population
* Nominal P < 0.05
Final data

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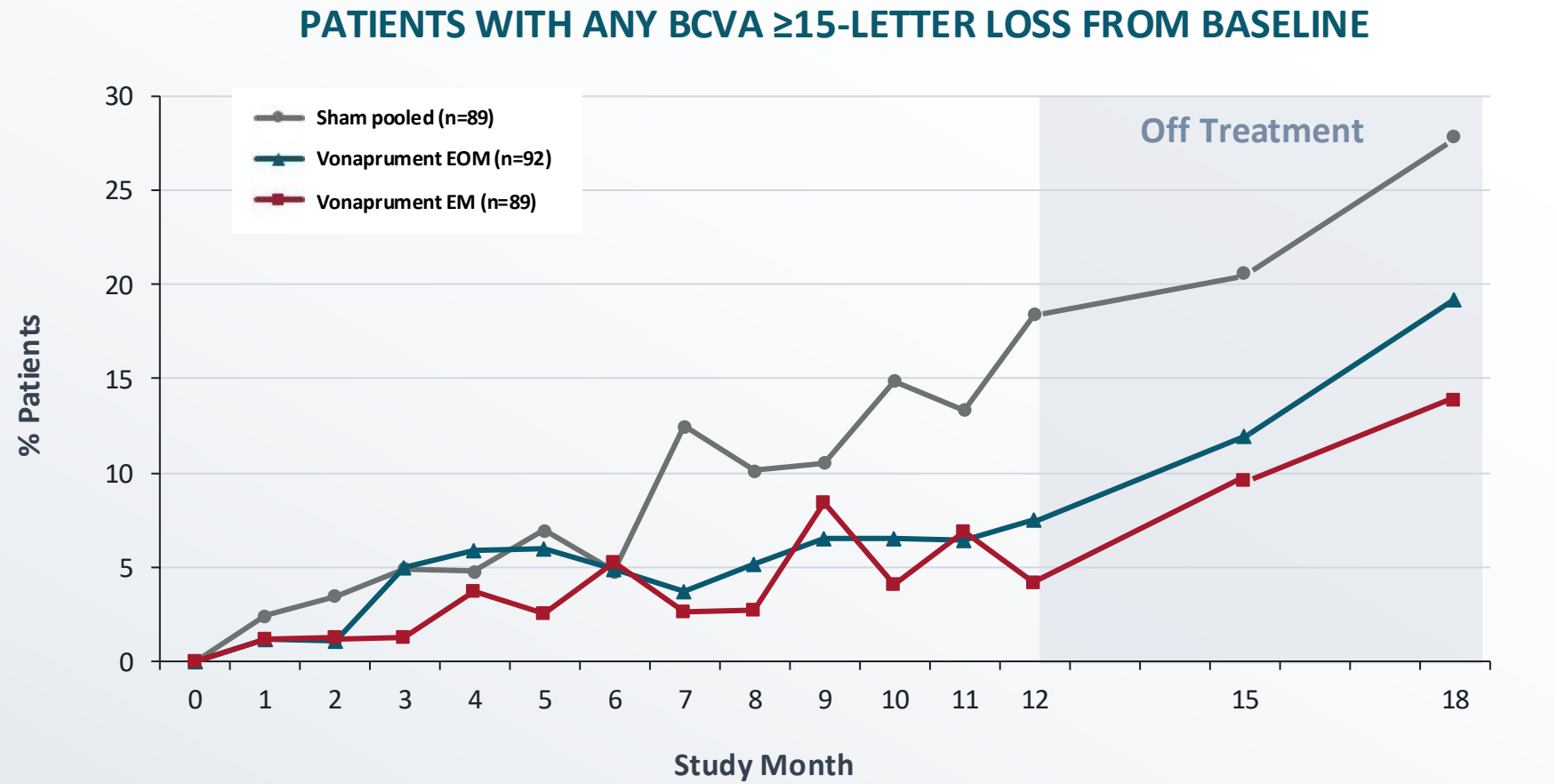
Proportion of Eyes With BCVA ≥15-Letter Loss Accelerated After Cessation of Treatment

Consistent with true on-treatment drug effect and disease-modifying mechanism of action



- Low frequency (<0.6% per month) of single BCVA ≥15-letter losses in EM- and EOM-treated groups during 12-month treatment period
- While benefit was maintained after treatment cessation the rate of BCVA≥15 LL increased to parallel that of sham (>1.6% per month)

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BCVA 15-Letter Change from Baseline Historically Used in Many Pivotal Trials

BEST CORRECTED VISUAL ACUITY (BCVA)

15-Letter Loss

Example: 20/60 to 20/120

PRODUCT	PRIMARY ENDPOINT MEASURE
Wet AMD	
Lucentis	Trial 1 & 2: BCVA ≥15 letter Trial 3 & 4: mean BCVA change
Eylea	BCVA ≥15 letter
Vabysmo	Mean BCVA change
DME	
Lucentis	BCVA ≥15 letter
Eylea	Mean BCVA change
Vabysmo	Mean BCVA change
Iluvien	BCVA ≥15 letter
Retinal Vascular Occlusion (BRVO/CRVO)	
Lucentis	BCVA ≥15 letter
Eylea	BCVA ≥15 letter
Ozurdex	BCVA ≥15 letter

ANNEXON biosciences

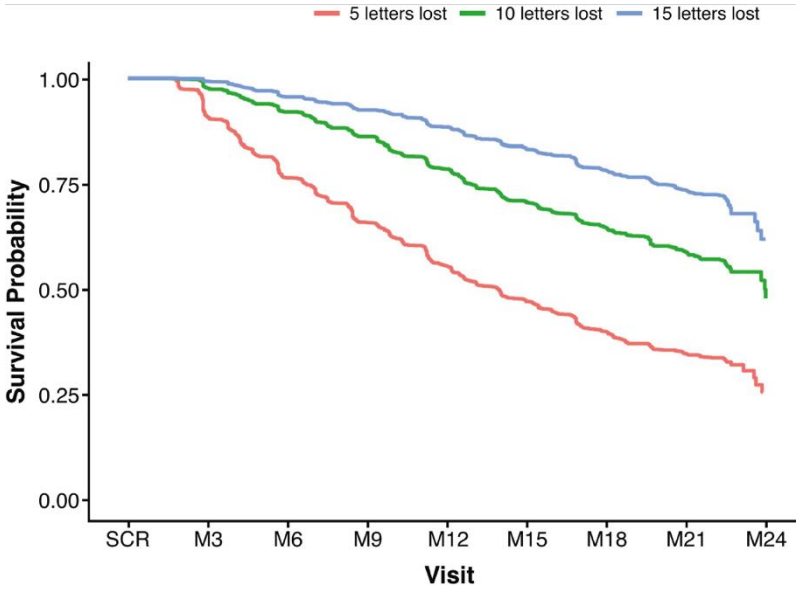
Visual Acuity Outcomes in GA from Previously Published Datasets

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Visual Loss in Geographic Atrophy

Learnings from the Lampalizumab Trials

Neha Anegondi, MTech,[1] Verena Steffen, MSc,[1] Srinivas R. Sadda, MD,[2,3] Steffen Schmitz-Valckenberg, MD,[4,5] Adnan Tufail, MD,[6,7] Karl Csaky, MD, PhD,[8] Eleonora M. Lad, MD, PhD,[9] Peter K. Kaiser, MD, FASRS,[10] Daniela Ferrara, MD, PhD,[1] Usha Chakravarthy, FRCOphth, PhD[11]

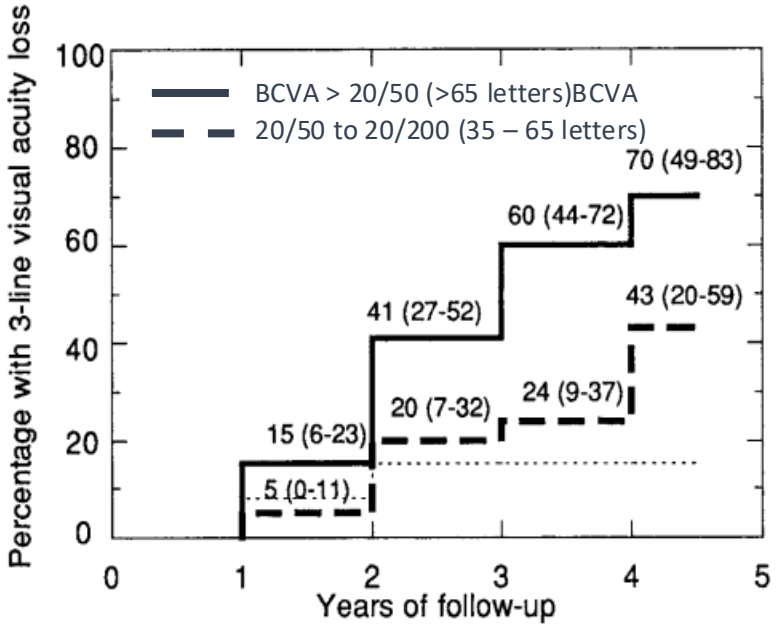


- >2000 eyes in the lampalizumab program
- Mean Baseline VA = 66 letters (~20/50)
- Mean Baseline GA Area = ~8.0 mm²
- ~25% had BCVA ≥15-LL at 2 years

Ophthalmology (2024)
https://doi.org/10.1016/j.ophtha.2024.11.017

Enlargement of Atrophy and Visual Acuity Loss in the Geographic Atrophy Form of Age-related Macular Degeneration

Janet S. Sunness, MD,[1,2] Joel Gonzalez–Baron, MD,[1] Carol A. Applegate, COT,[1] Neil M. Bressler, MD,[1–3] Yan Tian, BS,[3] Barbara Hawkins, PhD,[4] Yolanda Barron, MS,[4] Akiva Bergman, BTL[1]



- 123 GA patients; natural history study
- Median Baseline VA = 20/44
- Median Baseline GA Area 2.9 Disc Areas
- Vision Loss varied with BL VA, ~30% ≥15-LL at 2 years

Ophthalmology (1999)
doi:10.1016/S0161-6420(99)90340-8

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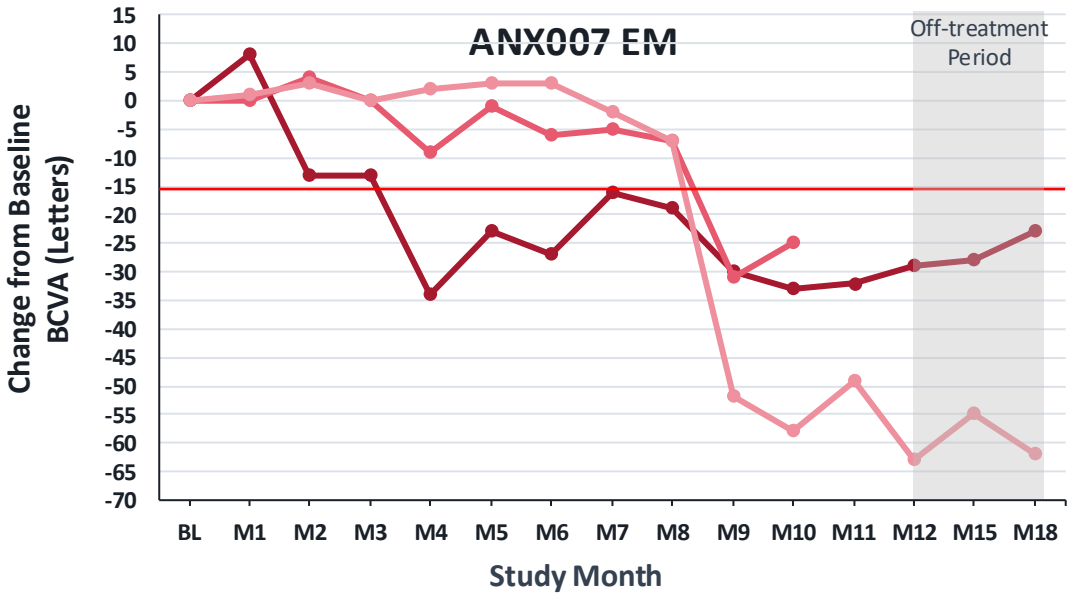
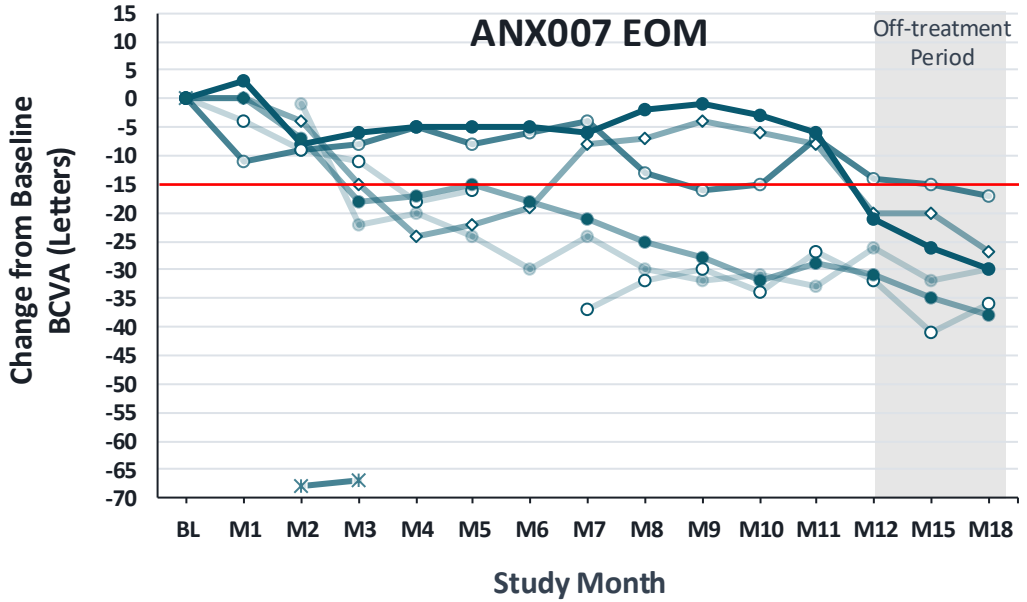
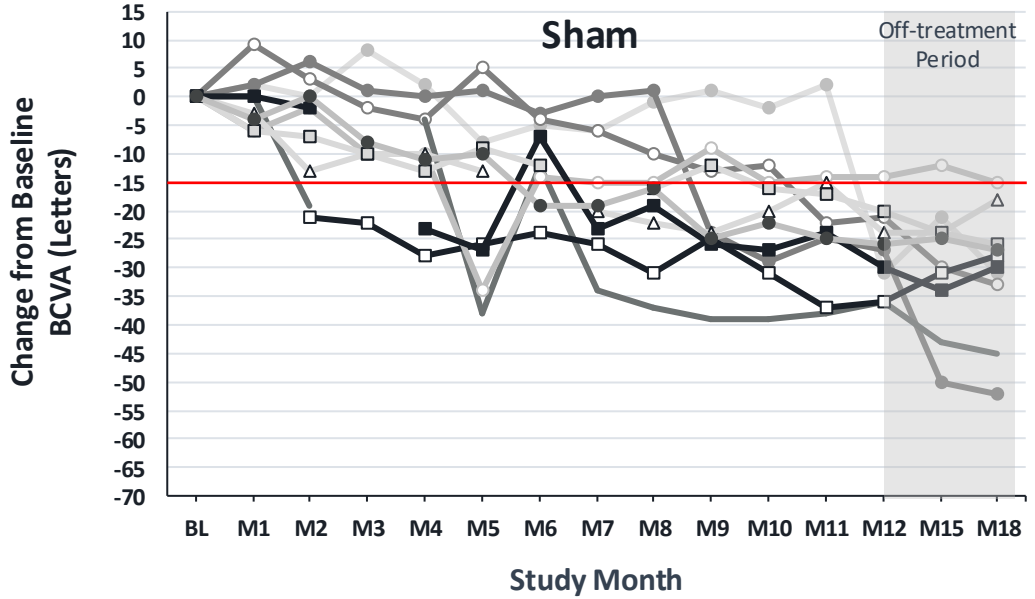
Subgroup* Analysis: Change From Baseline Through Month 18 in the ARCHER Study: ≥15-Letter Loss Group







BCVA ≥15-LL Definition:

2 Consecutive Visits during the treatment period; Month 12 loss confirmed at Month 15

*Subgroup of patients in ARCHER meeting ARCHER II vision eligibility requirements

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ARCHER: Key Safety Data

ADVERSE EVENTS OF SPECIAL INTEREST n (%)	SHAM (N=89)	VONAPRUMENT EM (N=89)	VONAPRUMENT EOM (N=92)
Choroidal Neovascularization	3 (3.4%)	4 (4.5%)	4 (4.3%)
Endophthalmitis	0	1 (1.1%)	2 (2.2%)
Retinal Vascular Occlusion	0	0	1^ (1.1%)
Retinal Vasculitis	0	0	0
Intraocular Inflammation+	0	2 (2.2%)	1 (1.1%)
Ischemic Optic Neuropathy+	0	0	0

INTRAOCULAR INFLAMMATION DETAILS* n

Iritis – 1
Resolved with topical steroids in 2 days
No Vasculitis

Vitritis – 1
Resolved with topical steroids in 9 days
No Vasculitis

Vitreous Debris – 1
KP on endothelium, prior treatment with topical steroids
No Vasculitis

*Event Verbatim term listed

^Isolated cilioretinal artery occlusion; no vasculitis confirmed by DSMC and reading center
+Not AESI, included because of current interest

Section Wrap-Up

- Data from clinical trials indicate that a meaningful proportion of dry AMD patients with GA can lose 15 or more ETDRS letters over 1 to 2 years

---

- In ARCHER, through 12 months, fewer patients lost ≥15 letters with monthly vonaprument treatment compared to sham, with a risk reduction of 73%
  - Trends were consistent across baseline characteristics and lesion phenotypes

---

- These trends towards visual acuity benefit were seen across several measures of visual acuity including Low Luminance Visual Acuity

---

- Safety Profile: No increase in CNV, no retinal vasculitis, no ION

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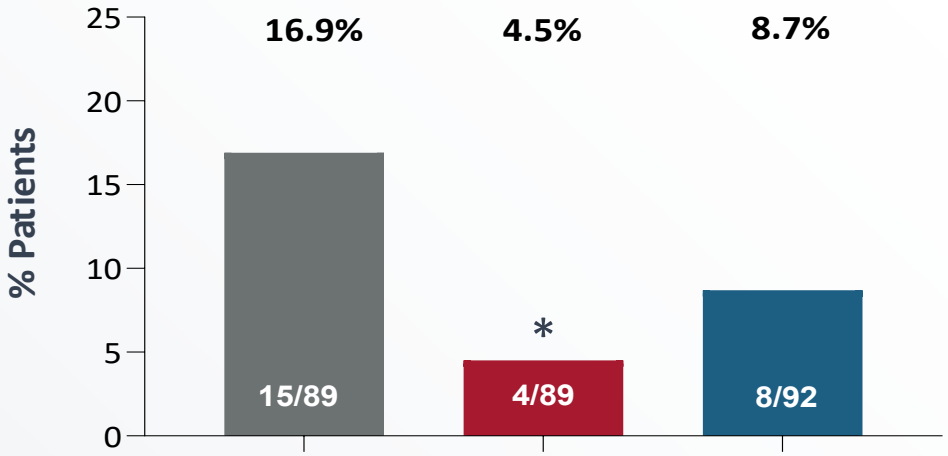
Connecting Structure and Function in the ARCHER trial

- Visual Acuity findings at baseline were associated with integrity of Ellipsoid Zone, an imaging biomarker reflecting the health and function of photoreceptors
- Treatment with vonaprument resulted in numerically greatest anatomic benefit in the macular center
- Primary Endpoint (GA lesion area) was missed but interesting trends were observed, consistent with proposed MOA of vonaprument

Fewer Vonaprument-Treated Eyes Had BCVA ≥15-Letter Loss vs. Sham, but GA lesion growth was not significantly different

PROPORTION OF PATIENTS WITH CONFIRMED BCVA ≥15-LETTER LOSS AT TWO CONSECUTIVE VISITS THROUGH MONTH 12*

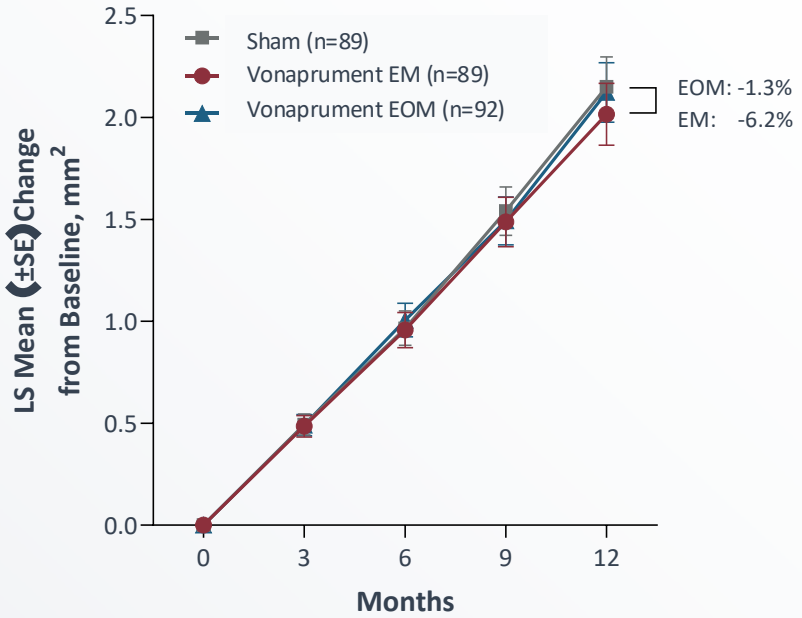


	Sham	Vonaprument EM	Vonaprument EOM
Nominal p-value vs Pooled Sham^	---	0.0076	0.0994

*BCVA ≥15-Letter Loss at Month 12 was confirmed at the subsequent visit (Month 15). In ARCHER, visits were monthly through Month 12 and then at Months 15 & 18

^Nominal p-value from a Chi-square test in ITT population: *Nominal p < 0.05

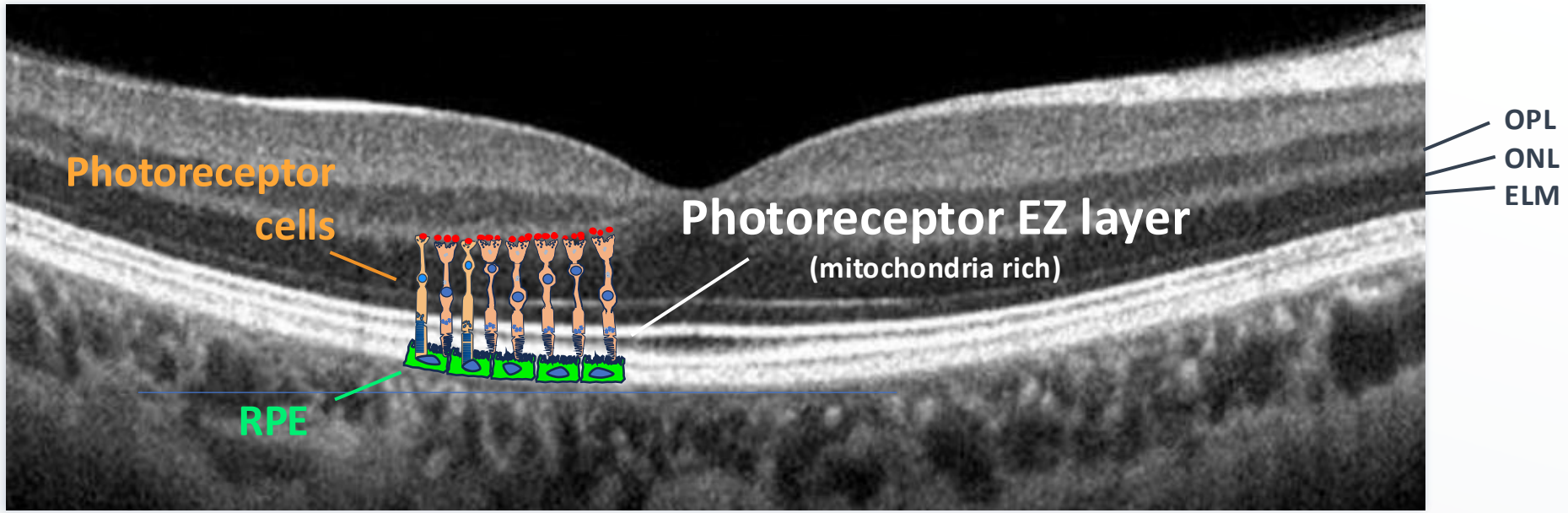
RPE LOSS FROM BASELINE TO MONTH 12 ALL ARCHER PATIENTS#



#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.

ANNEXON biosciences
Vonaprument, formerly ANX007

Ellipsoid Zone (EZ) Integrity: An Imaging Biomarker of Photoreceptor Health and Function



octscans.com

ARCHER EZ POPULATION

Sham	ANX007 EM	ANX007 EOM	Total
71	60	62	193

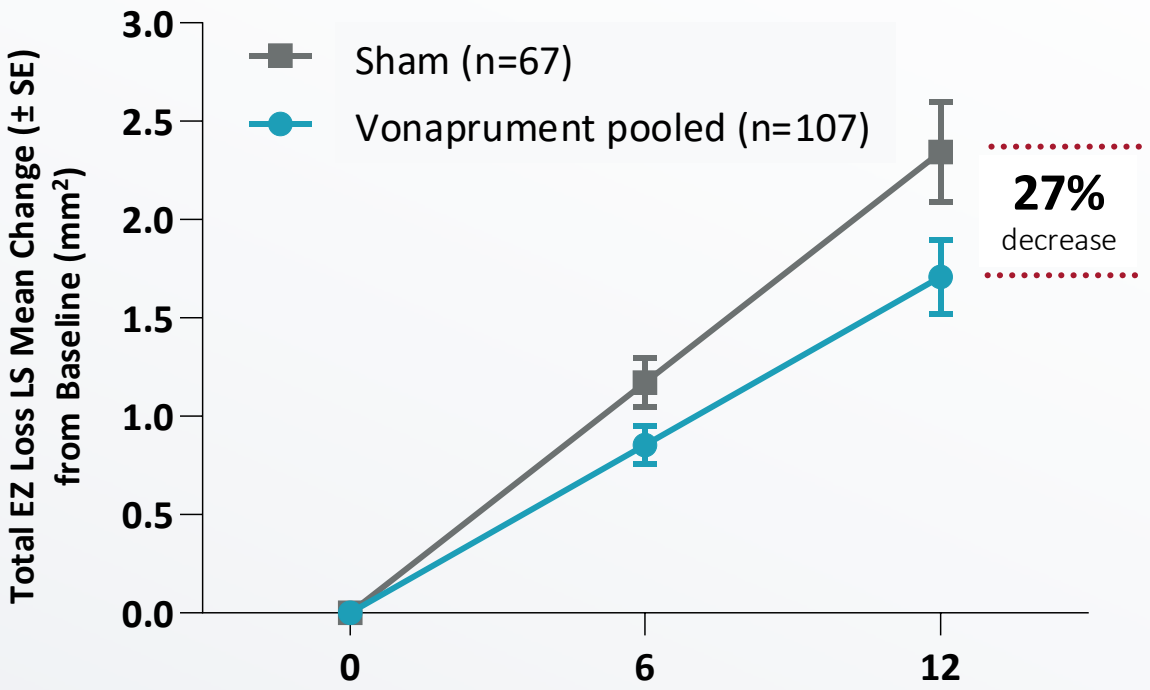
1 patient had OCT after injection and was therefore excluded

- 192 eyes with OCT scans from Heidelberg Spectralis
- Patient demographics and study eye characteristics were generally well balanced across groups; “Spectralis OCT” eyes were similar to overall population
- Same treatment effect between sham, EM and EOM groups as in whole study population

ANNEXON biosciences

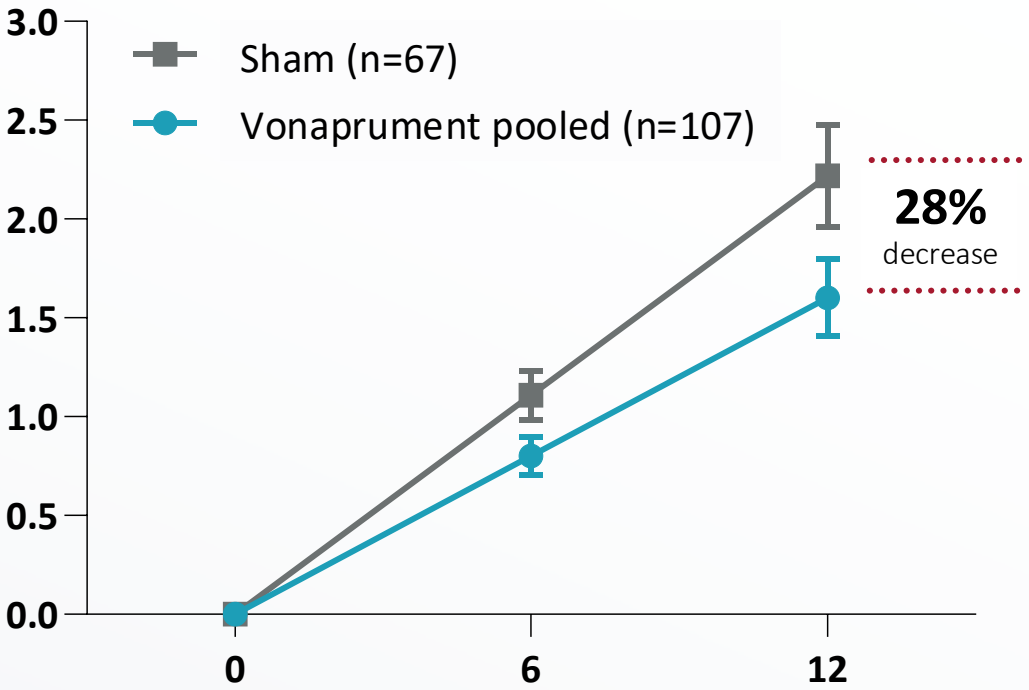
Ellipsoid Zone Total Loss and Attenuation Through 12 Months

EZ TOTAL LOSS (EZ = 0 µm thickness)



Nominal p-value vs sham^ ANX007 0.0457

EZ ATTENUATION (EZ < 20 µm thickness)



Nominal p-value vs sham^ ANX007 0.0595

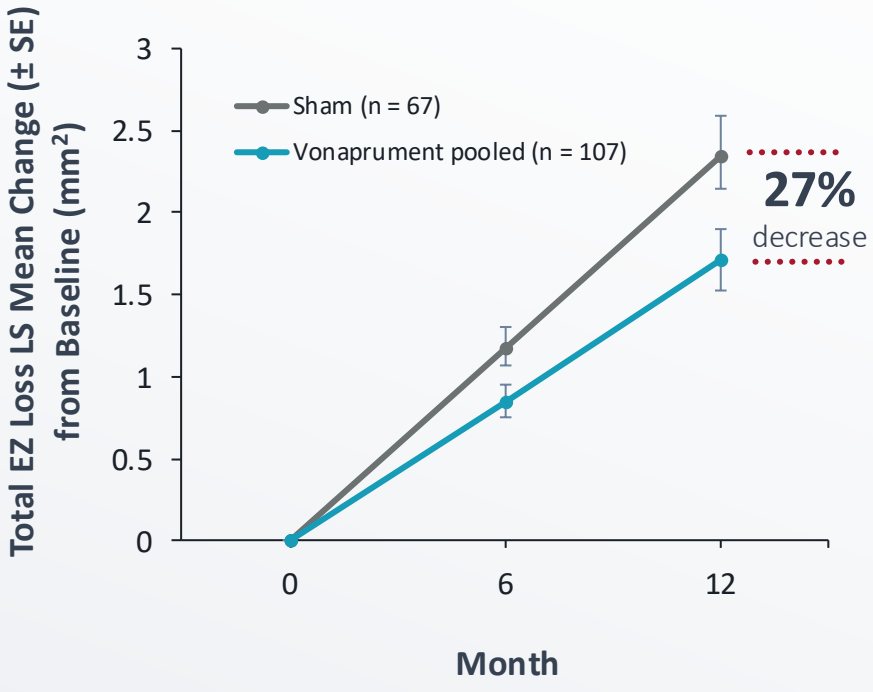
^Nominal p-values from a linear mixed model for repeated measures model (slope) analysis;
Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy/attenuation at baseline
Vonaprument treatment arms were not statistically different
Final data

ANNEXON biosciences

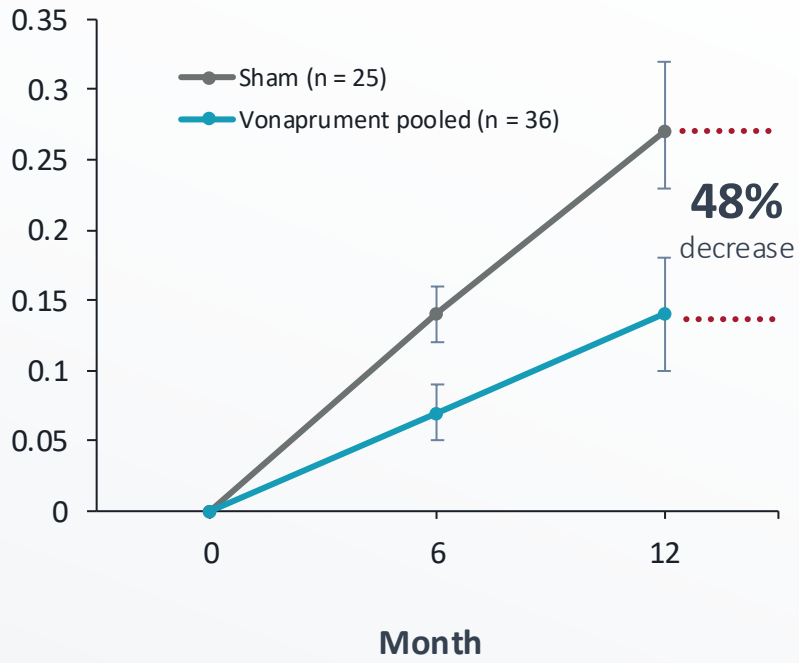
Area of Total Loss of Ellipsoid Zone Through Month 12

Numerically higher protection with vonaprument in central subfields compared to pan-macula

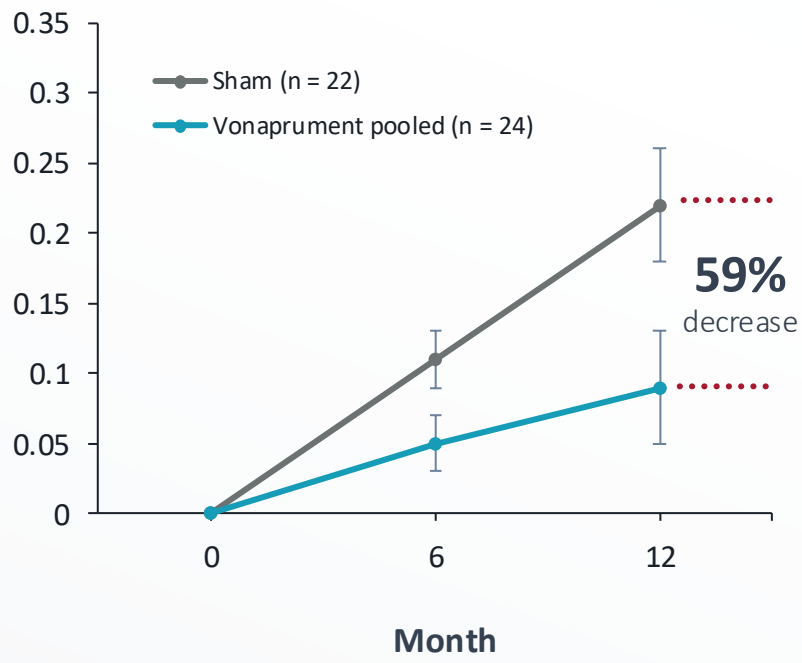
PAN-MACULA



CENTRAL 2.0 MM



CENTRAL 1.5 MM



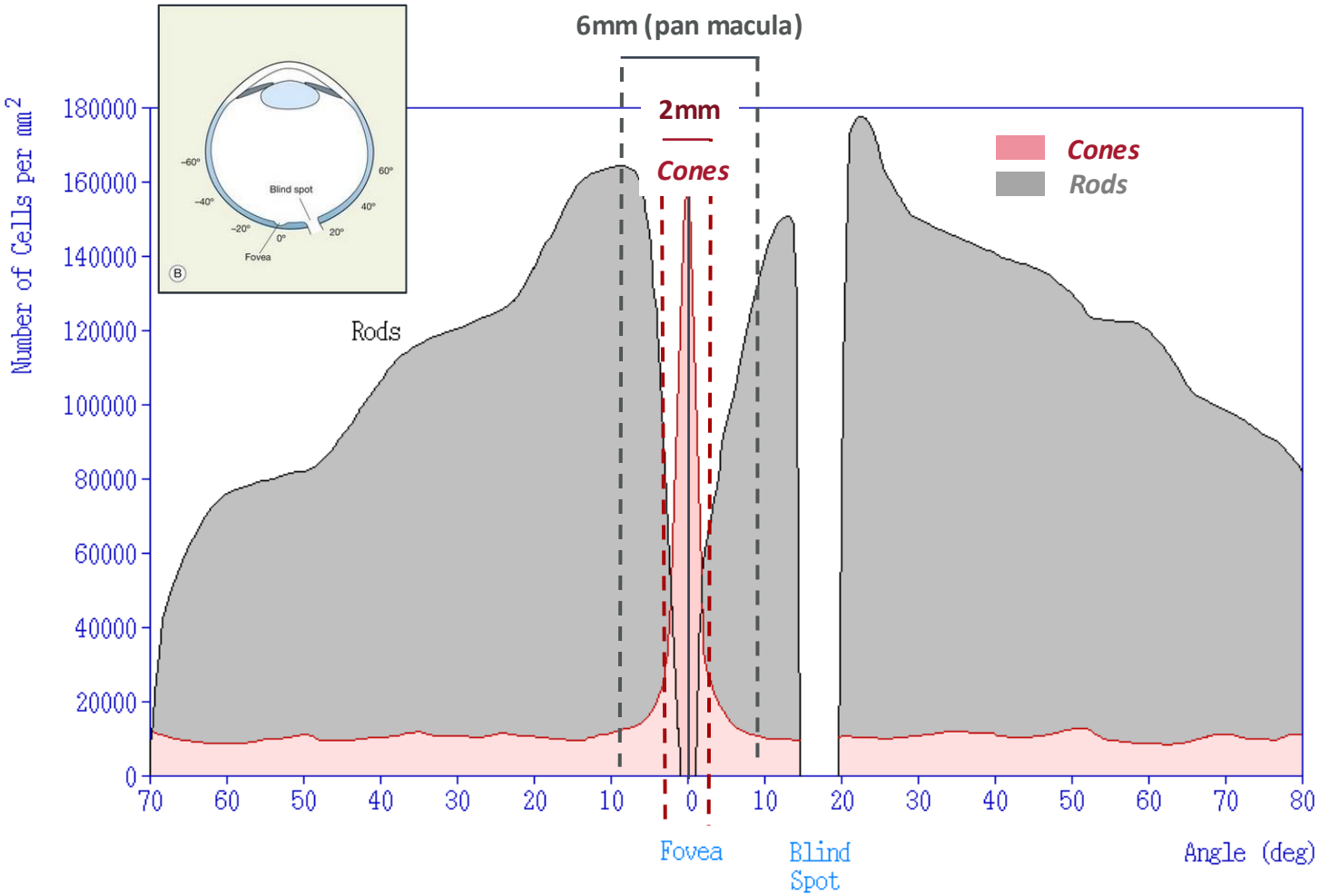
Nominal p-value^					
Vonaprument Pooled vs Sham	0.0457	Vonaprument Pooled vs Sham	0.0218	Vonaprument Pooled vs Sham	0.0319

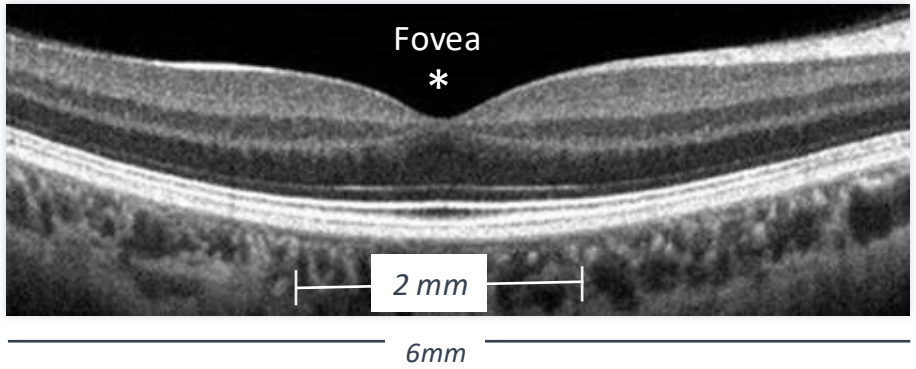
^Nominal p-values from a linear mixed model for repeated measures model (slope) analysis;
Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy/attenuation at baseline

ANNEXON biosciences

The Foveal Center, with its Dense Concentration of Exclusively Cones, is the Retinal Region Responsible for High-Resolution Vision

Protecting photoreceptor synapses in the fovea is fundamental to preserve visual acuity

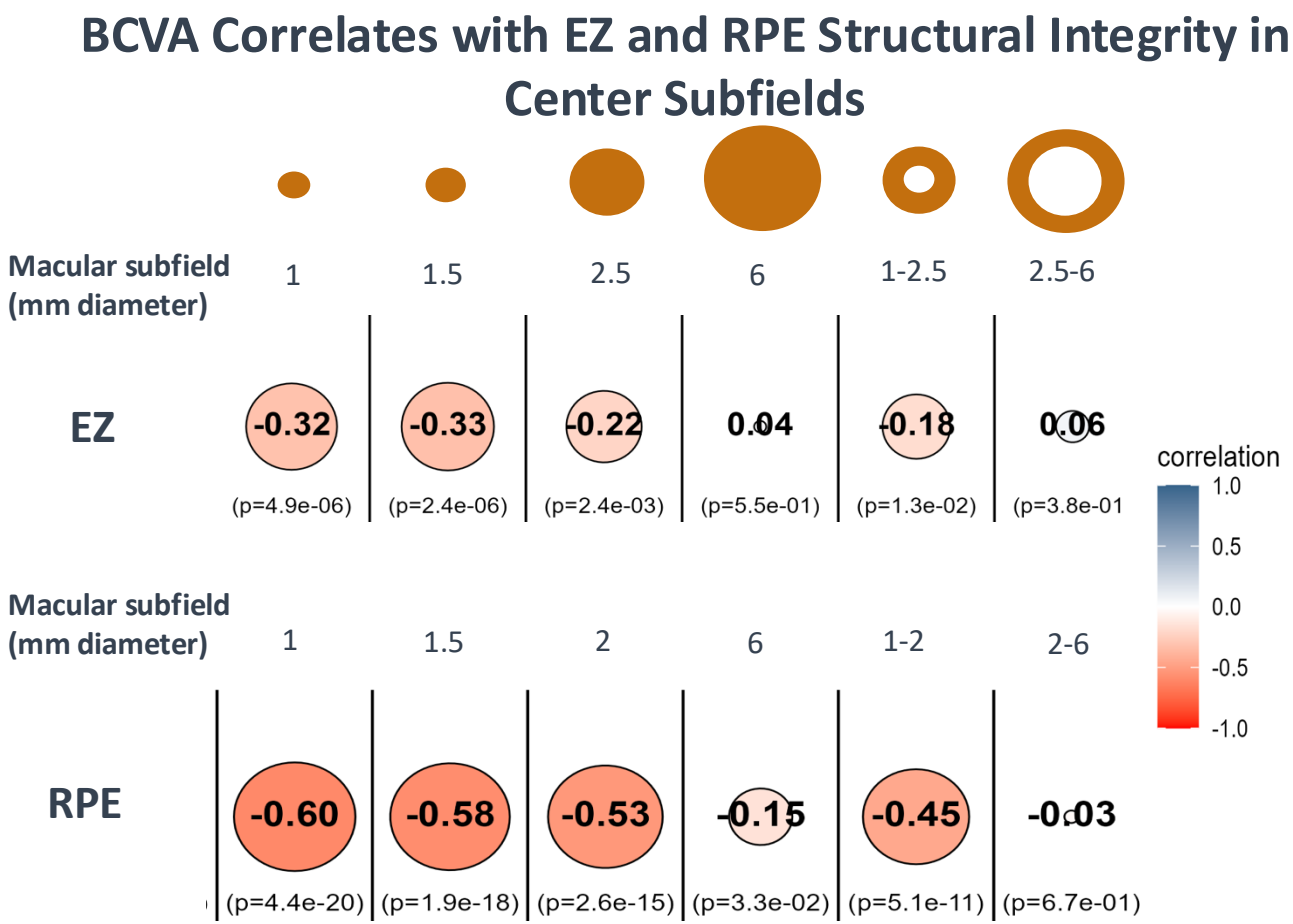




- **Subdomains within ~2mm** of the foveal center are populated almost exclusively by cones – **responsible for fine vision in bright light (photopic) conditions (BCVA)**
- Subdomains between 2 and 6mm from the foveal center are predominantly populated by rods – rods and cones working together are needed for vision in lower light (mesopic) conditions (LLVA)

ANNEXON biosciences

ARCHER Correlations Between Baseline BCVA & EZ and BCVA & RPE



Data: ARCHER, eyes with Spectralis OCT images (n=192), Baseline

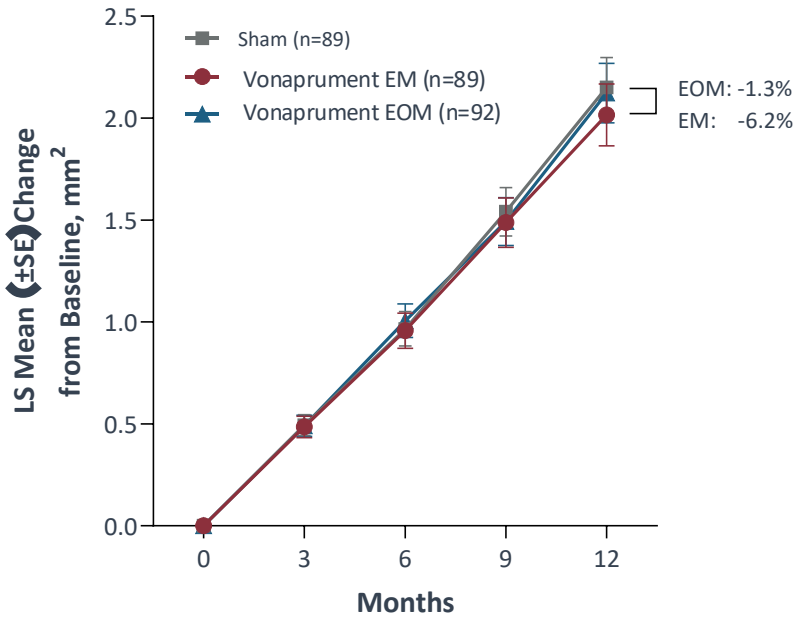
Post-hoc analysis; all p-values are nominal

ANNEXON biosciences

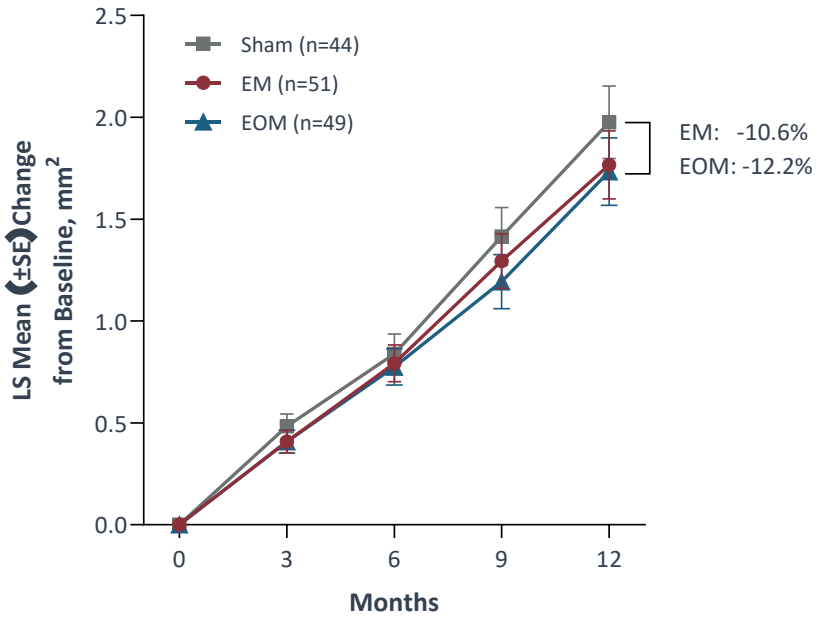
RPE Lesion Growth Through 12 Months

Greater RPE protection near foveal center

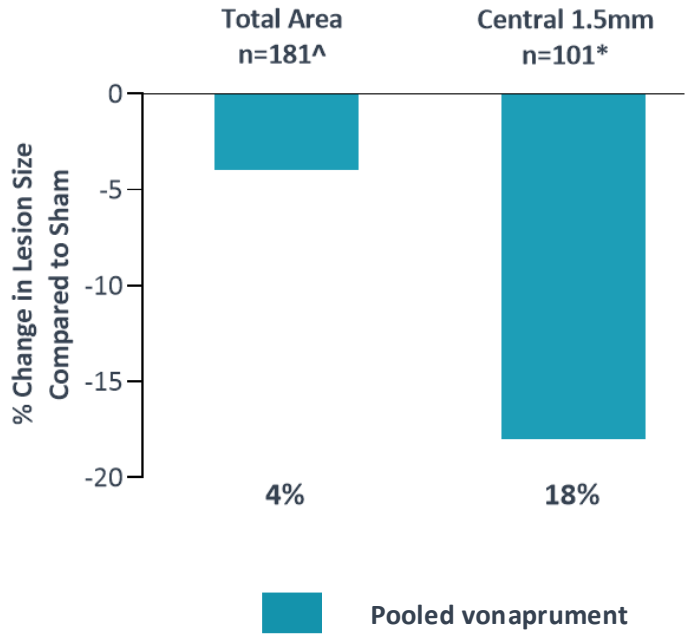
RPE Loss from Baseline to 12 months All ARCHER Patients#



RPE Loss from Baseline to 12 months ARCHER Sub-foveal Patients#



Change in RPE Loss at 12 months By Region#



#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.

#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

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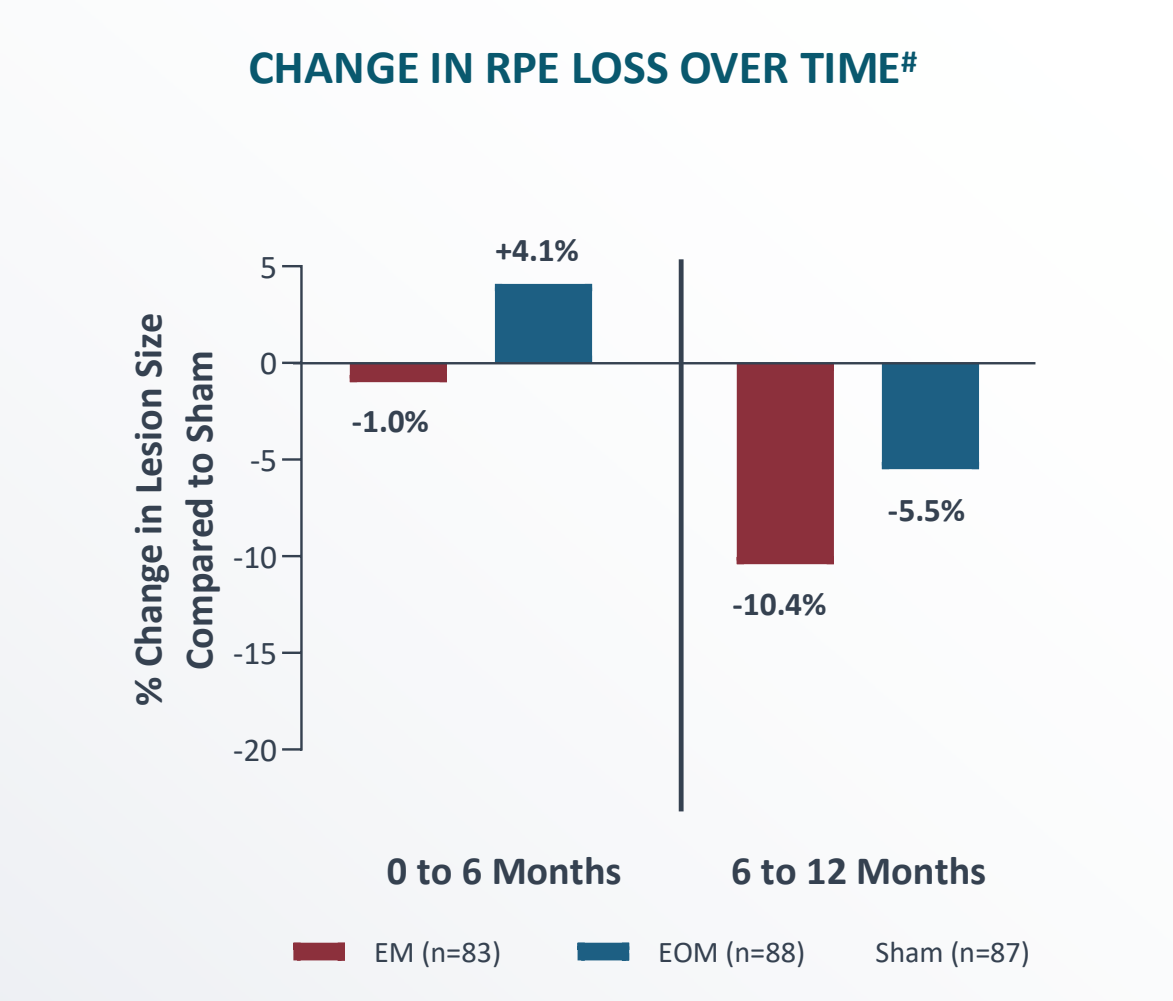
Reduction in RPE Loss Increased Over Time

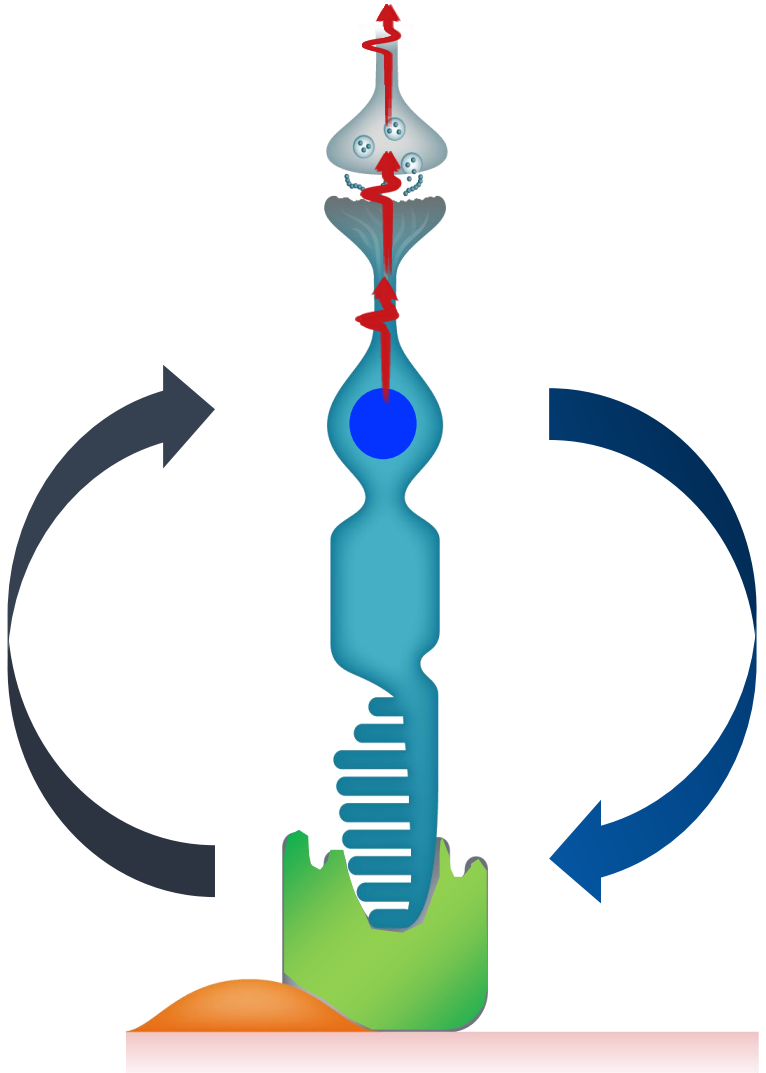


#Least-square (LS) mean and its standard error (SE) are based on a mixed-effect model for repeated measures (MMRM) adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.

Photoreceptors and RPE Cells Are a Symbiotic “Functional Unit”, Providing Bidirectional Trophic Support

RPE Cells Support PRs:

- Visual cycle: Retinoid recycling
- Phagocytosis of shed outer segments
- Nutrient and ion transport
- Secretion of growth and survival factors
- Oxidative stress management
- Immune and complement regulation



PRs Support RPE cells:

- Outer segment renewal (“Exercise” of RPE)
- Metabolic coupling
- Trophic factors (RdCVF)
- Regulation of outer-retinal vascular environment
- Anti-oxidant and redox crosstalk

Sinha, Naah, Al-Ubaidi et al, https://doi.org/10.1016/j.isci.2020.101004; Nandrot et al., Nat Genet 2000; Hall et al., Exp Eye Res 2001; Kanow et al., Cell Reports 2017

ANNEXON biosciences

Vonaprument Protects Vision by Protecting Photoreceptors; Lesion Growth Slows Over Time

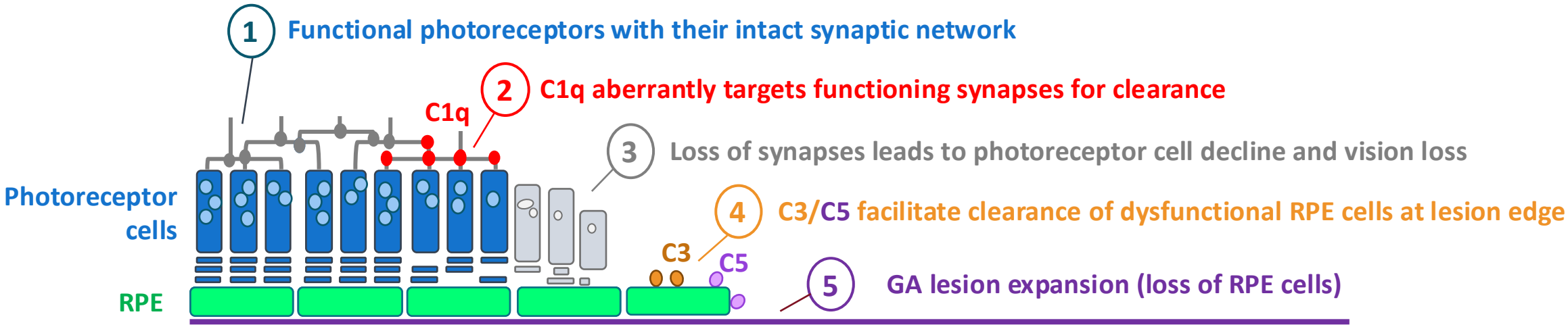
C1q inhibition protects photoreceptor synapses, cells and visual acuity via a defined neuroprotective mechanism[1]

- Protecting photoreceptors protects their associated RPE to slow lesion growth over time[2]
- Leaves lectin and alternative pathways in place[1] for clearance of dysfunctional RPE at lesion edge

Distinct from C3/C5 inhibition that slows lesion growth without demonstrating protection of visual acuity

- Blocks complement-dependent removal of dysfunctional cells[3] at lesion edge, but these cells don't contribute to vision
- Dysfunctional RPE cells make angiogenic factors that can contribute to abnormal blood vessel growth / CNV[4]

Sequence of GA Progression: Photoreceptor synapse and cell loss drives loss of vision[1], followed by loss of supporting RPE cells with expansion of the RPE/GA lesion[5]



[1]Yednock, et al, 2022 International *J Retin and Vitreous* **8**:79; [2]Heier, et al, submitted 2025; [3]Merle, et al., 2015 *Front Immunol* **6**:262; [4]Paterson, et al., 2023 *Molecular Vision* **29**:87-101; Farjood et al. 2020 *J Biol Eng* **14**:13; [5]Ehlers and Wykoff *Retina Today* Nov/Dec 2024; Pfau, et al., 2020 10.1001/jamaophthalmol.2020.2914

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Section Wrap-Up

- The center 2 mm of the macula features densely packed cone photoreceptors responsible for detailed, fine visual acuity tasks

- Visual acuity loss in dry AMD with geographic atrophy occurs due to damage to of these centrally located cone photoreceptors, which can be evaluated on OCT as loss of the Ellipsoid Zone

- Vonaprument has uniquely demonstrated consistent vision protection in multiple visual acuity measures in patients with dry AMD with GA

- Vonaprument also reduced loss of the ellipsoid zone, providing objective structural support for the visual function protection outcomes

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Vonaprument: Inhibitor of C1q to Treat Geographic Atrophy

Vonaprument

IVT administered antigen-binding fragment (Fab)

KEY ATTRIBUTES

- ✓ **Design: Modeled after established IVT-administered Fab antibodies**; **same antigen recognition structure as tanruprabart (ANX005)** – full length anti-C1q antibody well tolerated as IV treatment in GBS
- ✓ **Profile:** 50kD Fab antibody; **low viscosity / non-pegylated**; <10 pM potency formulated for intravitreal administration
- ✓ **Dosing:** 5 mg / **25 microliter volume**
- ✓ **Specificity: Full target engagement** / inhibition of C1q and the classical complement pathway observed; **lectin and alternative pathway remain in place** for immune and homeostatic functions[1]

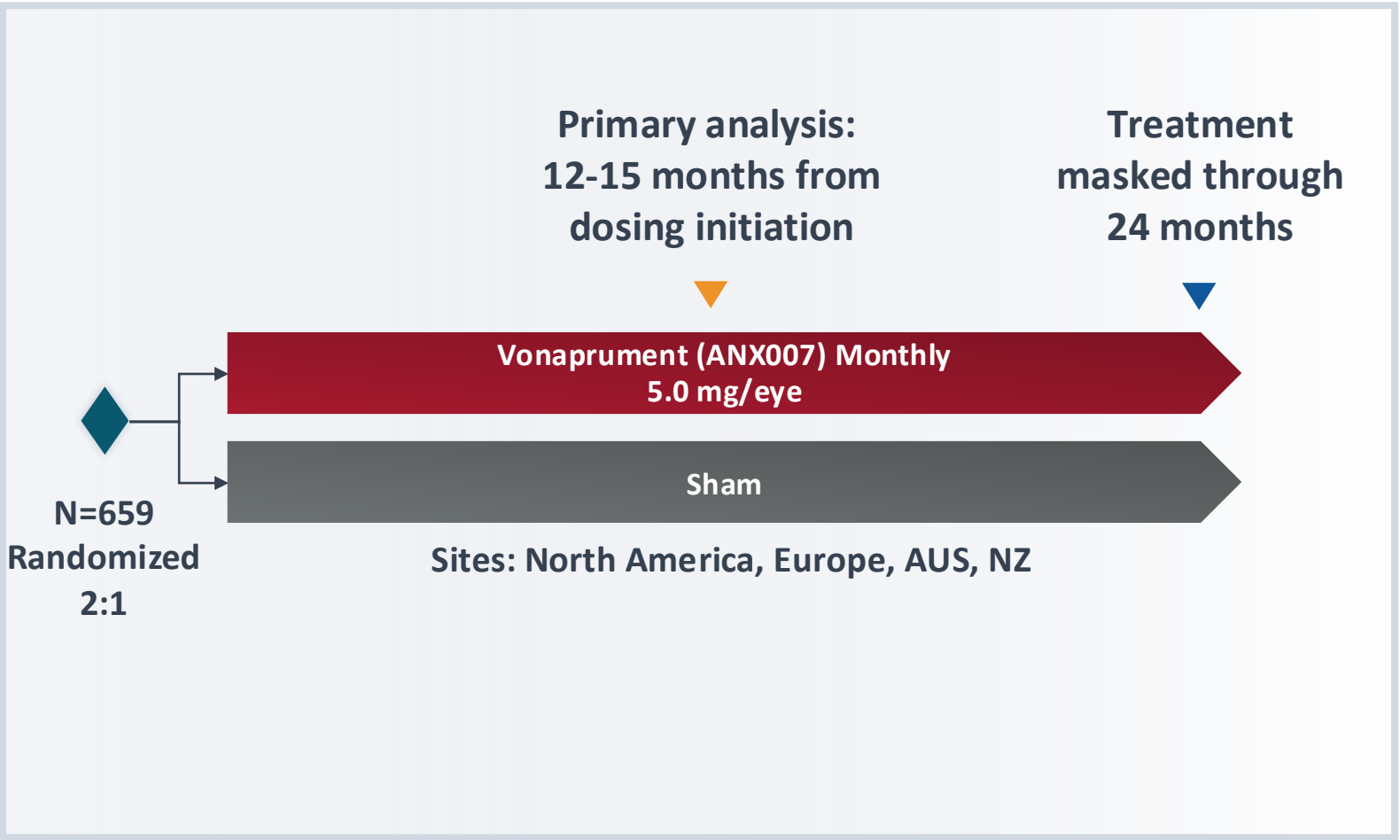
[1]Sun, et al., 2023 Ophthal Sci 3(2):100290

ANNEXON biosciences

ARCHER II Phase 3 Program –Fully Enrolled; Top Line Data Anticipated late 2026

Path to global filings with FDA and EMA

EMA PRIME designation and PDC selection; FDA Fast Track designation



PRIMARY ENDPOINT

Proportion of patients who experience a BCVA ≥15-Letter Loss confirmed at two consecutive visits

SECONDARY ENDPOINTS

Safety, LLVA, EZ integrity

Single-study program analyzed as two sub-studies addresses FDA two-trial recommendation.

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