Efficacy and Safety of Intravitreal Administration of ANX007 in Patients With Geographic Atrophy: Results of the ARCHER Phase 2 Study

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On behalf of the ARCHER Investigators

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Disclosures

Scientific Advisor:
4-DMT, Alexion, Allegro, Annexon, Apellis, Aspen Neuroscience, Blue Rock, Boehringer Ingelheim, Broadwing Bio, Complement Therapeutics, Emmecell, Galimedix, IVERIC Bio/Astellas, Janssen, Kriya Therapeutics, LumiThera, Lutronic Vision, Nanoscope Therapeutics, NGM Biopharmaceuticals, Novartis, Ocular Therapeutics, Osanni Bio, Perceive Bio, Regeneron, Retrotope, Roche, Sanofi, Thea Laboratoires

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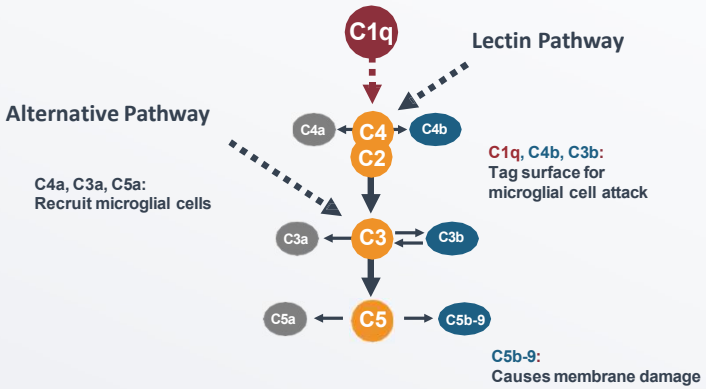
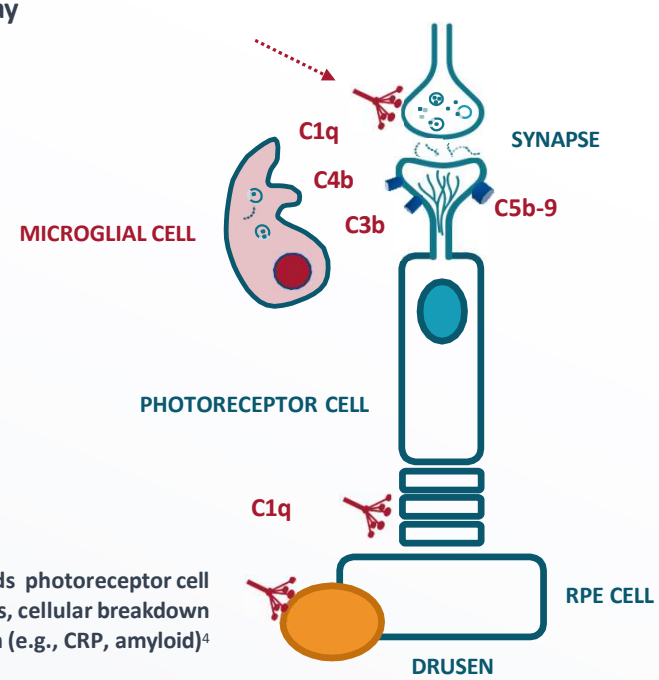
Anti-C1q: A Unique Neuroprotective Mechanism

C1q initiates the classical complement cascade to drive photoreceptor synapse loss, cell loss and neuroinflammation

- C1q is a **key driver of neurodegeneration**[1]
- C1q anchors classical pathway activation on **photoreceptor cells to cause inflammation and loss**[2]
- **ANX007 inhibits C1q** and all damaging components of the classical pathway[3]



C1q binds stressed photoreceptor synapses and activates the classical pathway



In GA, **C1q** also binds photoreceptor cell outer segments, cellular breakdown products and drusen (e.g., CRP, amyloid)[4]

[1]Stevens, 2007, *Cell* **131**:1164; Howell, et al., 2011 *J Clin Invest*. **121**:1429; Schafer, et al., 2012 *Neuron* **74**: 691; Stephan et al., 2012 *Annu Rev Neurosci* **35**:369; Hong, et al., 2016 *Science*. **352**:712; Lui, et al., 2016 *Cell* **165**:921; Dejanovic, et al., 2018 *Neuron* **100**:1322; Vukojicic , et al., 2019, *Cell Rep.* **29**:3087; Williams, et al., 2016 *Mol Neurodegener* **11**:26; [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

Photoreceptor Cells, Synapses & Function Are Lost Prior to RPE in GA

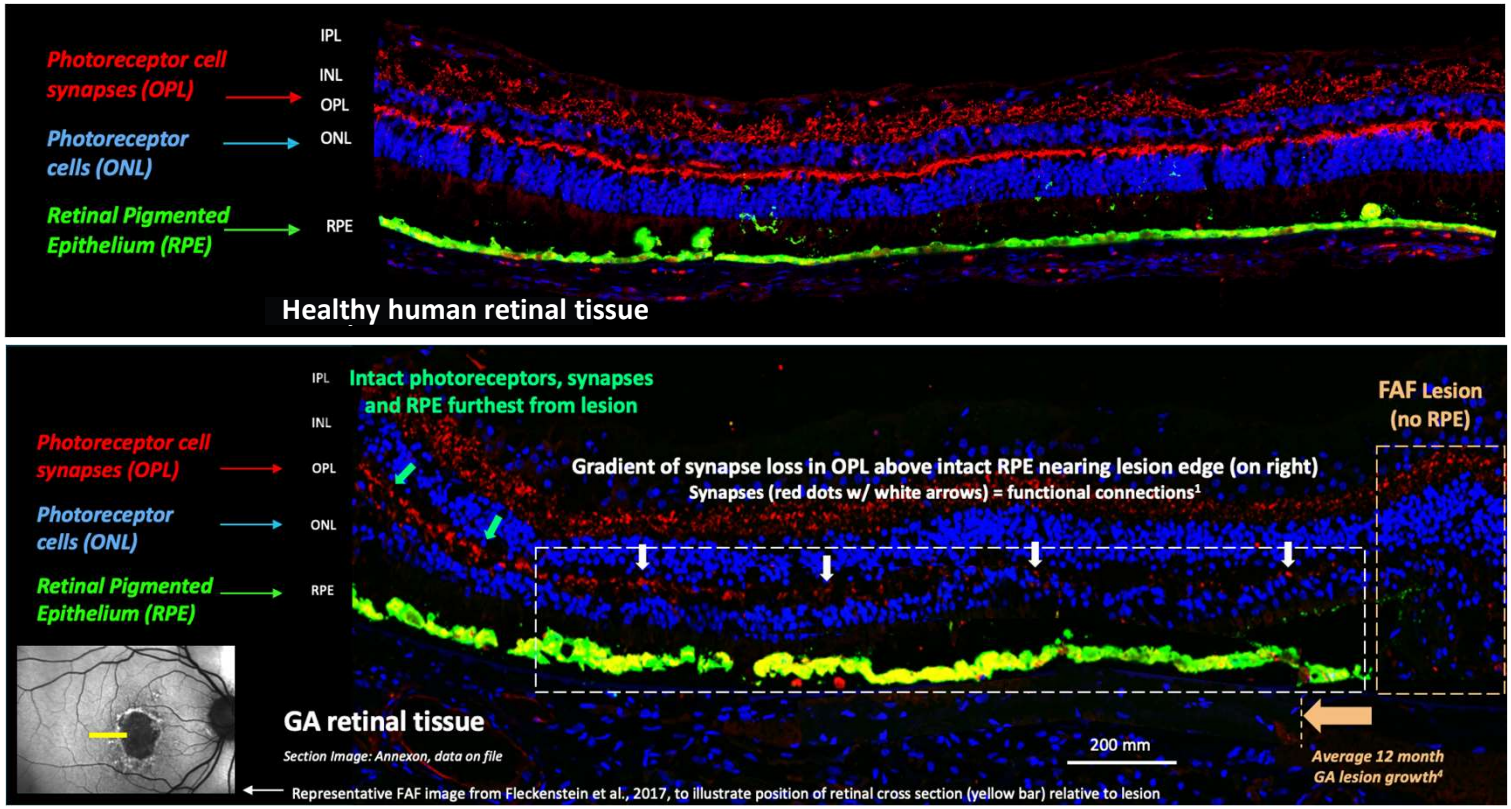
Blocking C1q protects photoreceptor cells and function upstream of RPE loss

Healthy Human Retina (top)

- Uniform layer of photoreceptor synapses (red) and photoreceptor neurons (blue)

GA Patient Retina (Bottom)

- Decreasing gradient of synapses and neurons (within white box) moving right toward lesion
- 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]



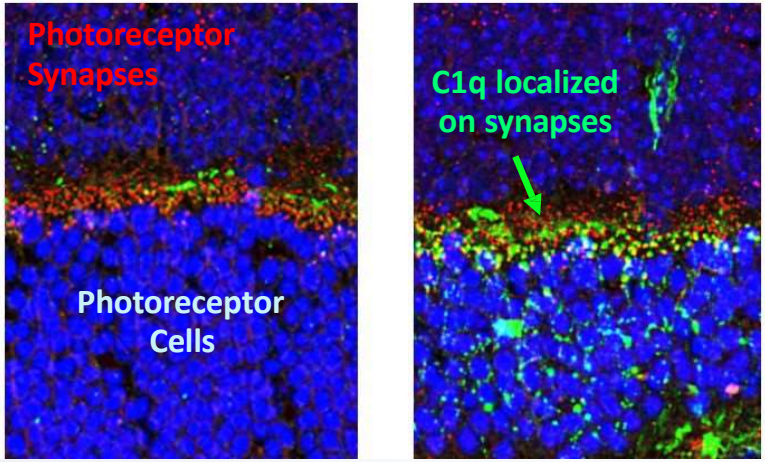
[1]Bird et al., 2014 *JAMA Ophthalmol* doi:10.1001/jamaophthalmol.2013.5799; Li, et al., 2018 *Retina* 38:1937; Pfau, et al., 2020 10.1001/jamaophthalmol.2020.2914; Sarks, et al., 1988 *Eye* 2:552; [2]Selkoe, 2002 doi: 10.1126/science.1074069; Burger, et al., doi.org/10.1016/j.ydbio.2021.04.001; [3]Heier,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

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

C1q Deposition on Photoreceptor Cells and Synapses with Light-Induced Damage

CONTROL

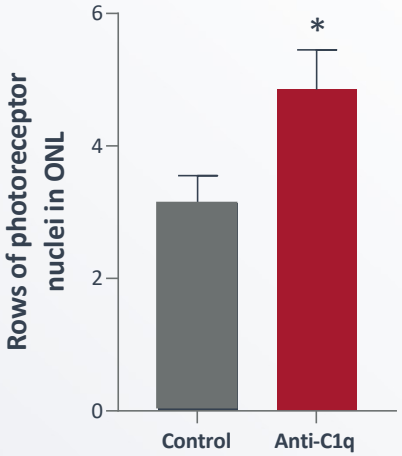
3 DAYS POST WHITE LIGHT DAMAGE



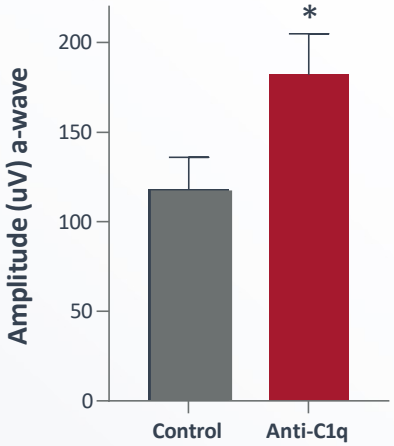
Annexon data on file

Anti-C1q Protected Photoreceptors and Function

ANTI-C1Q PROTECTED PHOTORECEPTOR CELLS/ RETINAL THICKNESS



PROTECTED RETINAL FUNCTION



Jiao, et al., 2018 *Mol Neurodegener* 13(1):45

ARCHER: ANX007 Phase 2 Trial in GA

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

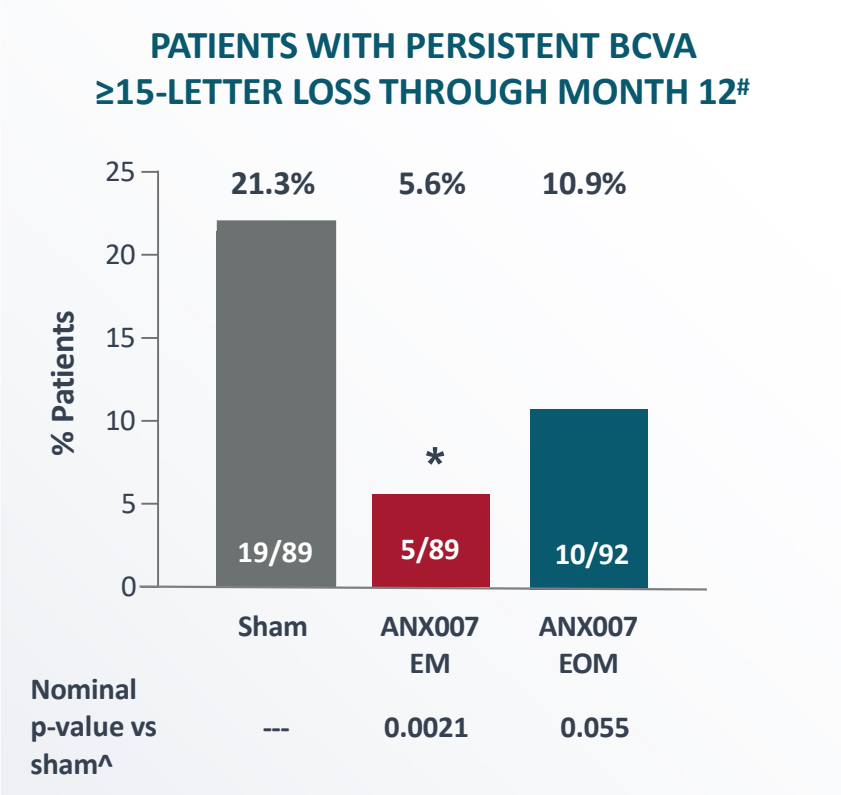
PRESPECIFIED SECONDARY FUNCTIONAL ENDPOINTS

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

Off-treatment
(6 months)

END OF STUDY
Month 18

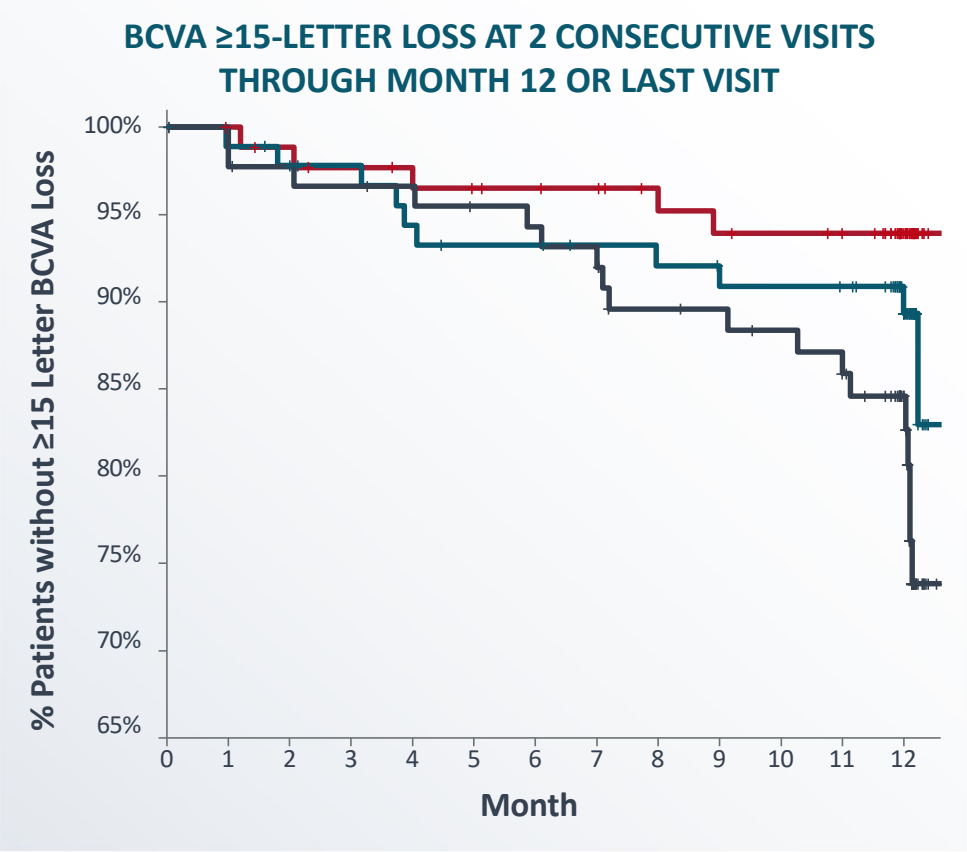
ANX007 Demonstrated Statistically Significant Protection From Vision Loss as Measured by BCVA ≥15-Letter Loss



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

- First known significant preservation of vision in GA
- Dose-dependent response informative
- BCVA ≥15-letter loss universally deemed clinically meaningful

Significant, Time-Dependent Protection From ≥15 Letter Vision Loss with ANX007 Monthly Treatment



EM (n=89)

72% Risk Reduction ANX007 EM

HR (CI) = 0.28 (0.11 to 0.76)
p = 0.006

EOM (n=92)

48% Risk Reduction ANX007 EOM

HR (CI) = 0.52 (0.24 to 1.13)
p = 0.064

Sham (n=89)

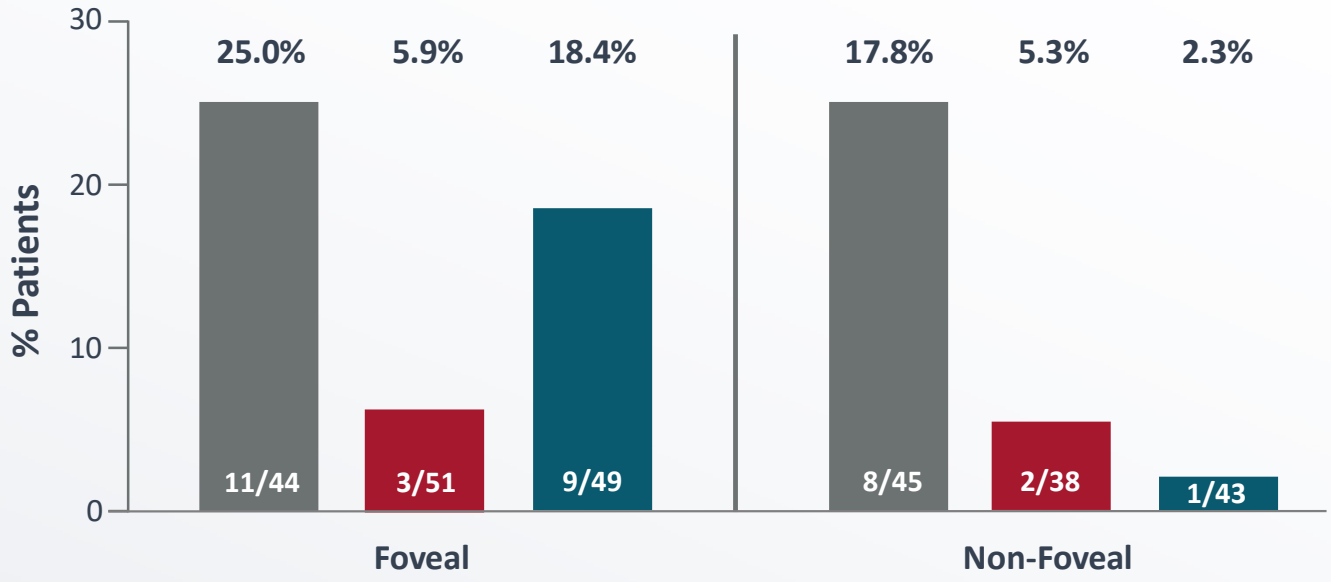
Sensitivity analysis confirmed treatment effect:

Significant 73% reduction in risk in EM group when 15 letter loss at Month 12 is confirmed at Month 15 visit

HR, hazard ratio; Nominal log-rank test (versus Sham) p-values are presented

Increasing ANX007 Impact Over Time

ANX007 BCVA Subgroup Analysis: Protection from Vision Loss in Foveal and Non-Foveal Patients

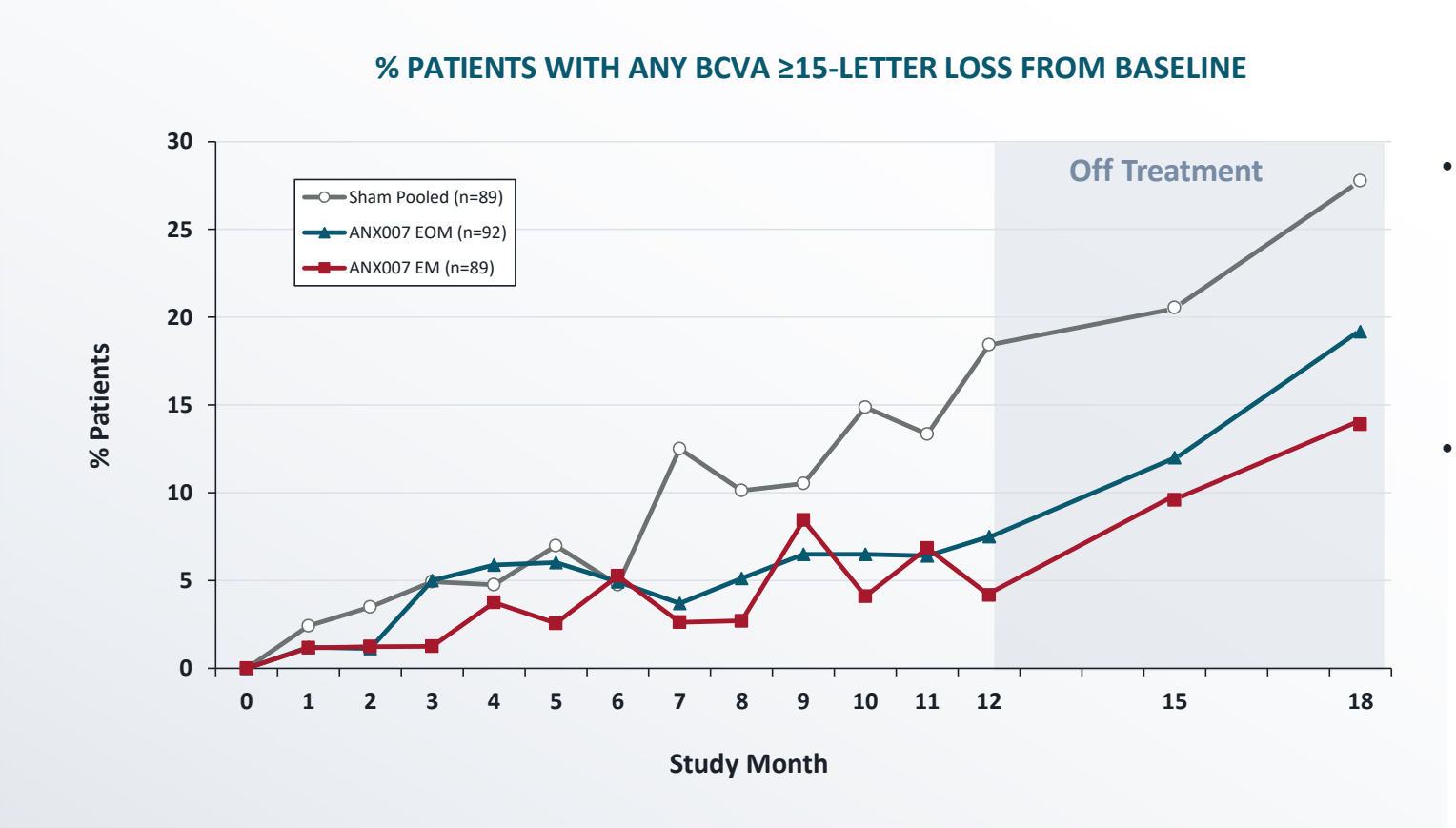


Nominal summary p-value vs. sham^	
ANX007 EM	0.0019
ANX007 EOM	0.0439

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

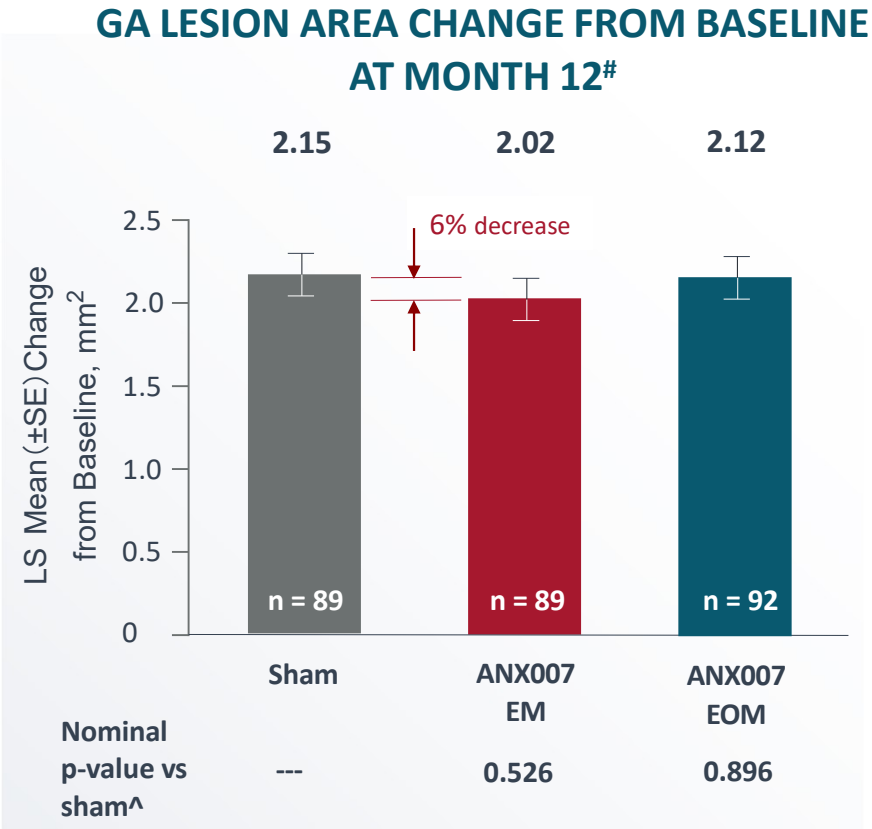
BCVA ≥15-Letter Loss Accelerates After Cessation of Treatment

Visual Function Loss Parallels Sham in Off-Treatment Period



- Low frequency (<10% per timepoint) of single BCVA ≥15-letter losses in EM- and EOM-treated groups during 12-month treatment period
- BCVA ≥15-letter loss frequency increased (10% or greater) in off-treatment period for EM and EOM groups, paralleling sham behavior

ANX007 Did Not Significantly Reduce GA Lesion Area

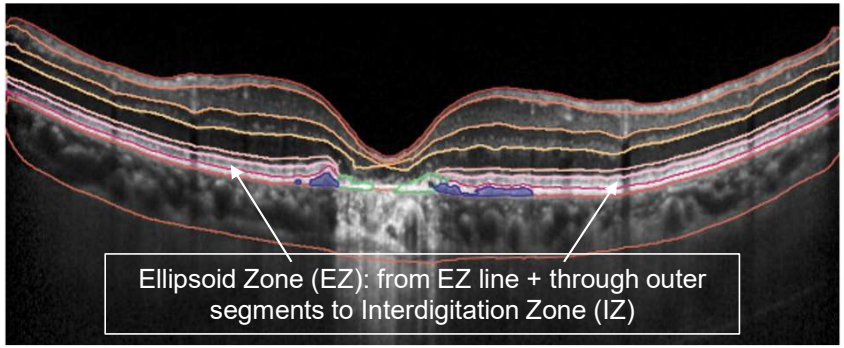


#The least-square (LS) mean, its standard error (SE), and p-value are based on a mixed-effect model for repeated measures (MMRM) adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction; ^2-arm MMRM model

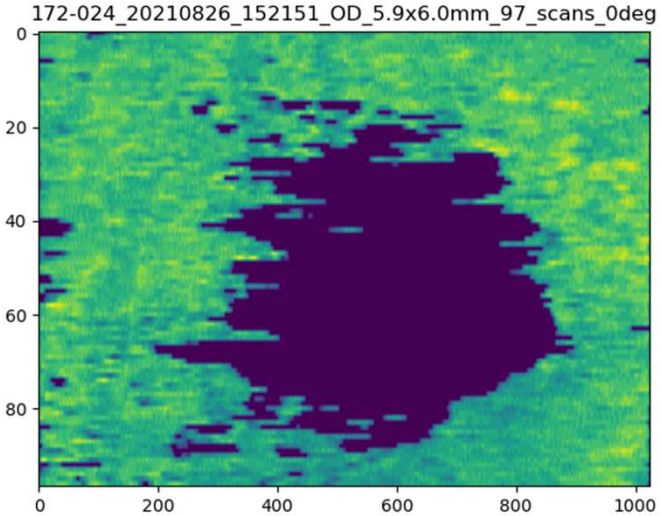
Ellipsoid Zone (EZ) Change Directly Measures Photoreceptor Anatomy Rather than RPE

Protection of photoreceptors may arise from synaptic protection

OCT



AI-Derived En Face Defect Surface Map



ARCHER EZ Population

- 194 patients with OCT scans from Heidelberg Spectralis

Sham	ANX007 EM	ANX007 EOM	Total
72	61	61	194

- Patient demographics and study eye characteristics were generally well balanced across the groups

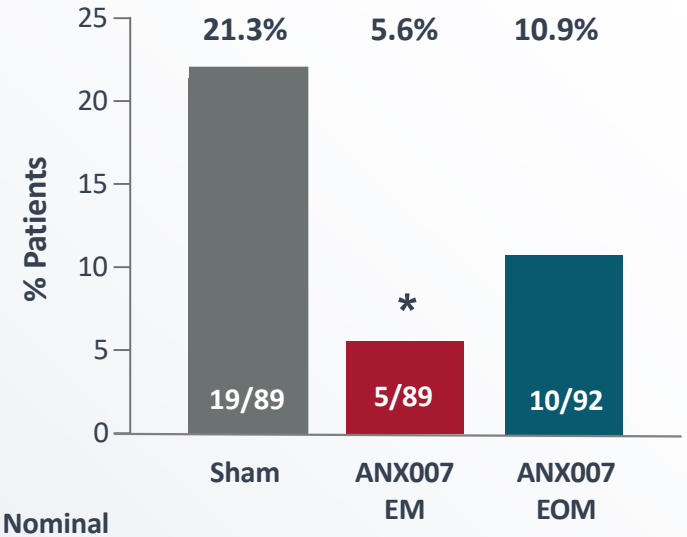
EZ Deficit Definitions

Total EZ Attenuation (FDA approvable Endpoint)	Defect map area with **EZ thickness = 0 µm**; complete loss of EZ visualization
Partial EZ Attenuation	Defect map area with **EZ thickness < 20 µm**; marker for earlier photoreceptor degenerative changes

Similar Protection from Vision Loss Across Total ARCHER Subjects and EZ Population

Total ARCHER Cohort

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

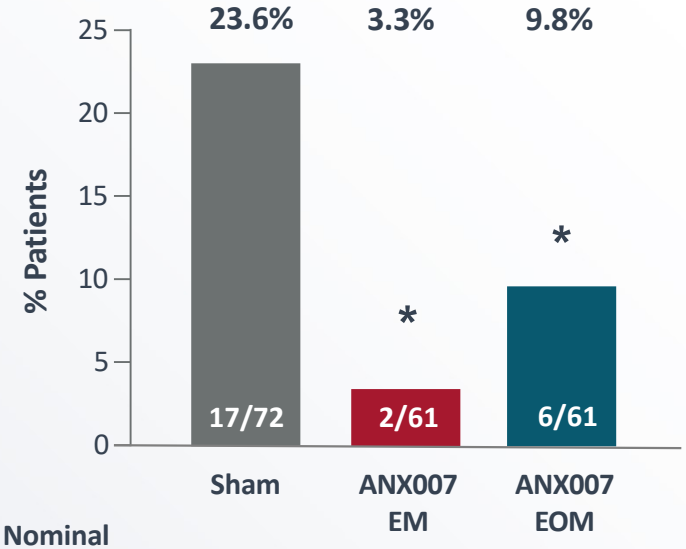


	Sham	ANX007 EM	ANX007 EOM
Nominal p-value vs sham^	---	0.0021	0.055

#Persistent for two consecutive visits through month 12 or at last visit
^Nominal p-value from a Chi-square test in ITT population (n = 270)
** Nominal p < 0.05*

EZ Population Only

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

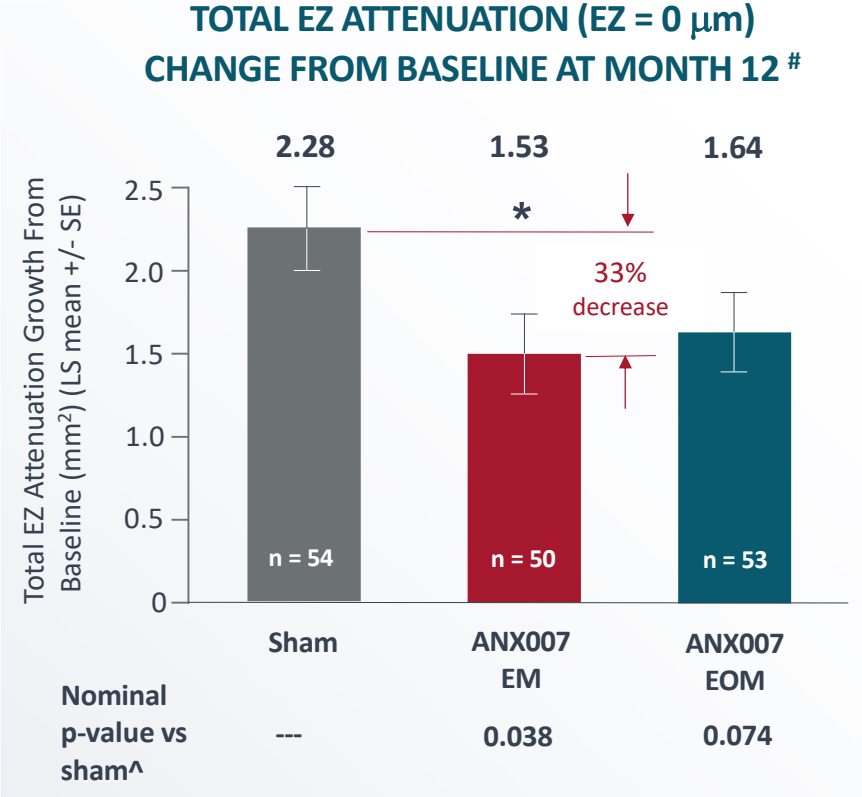


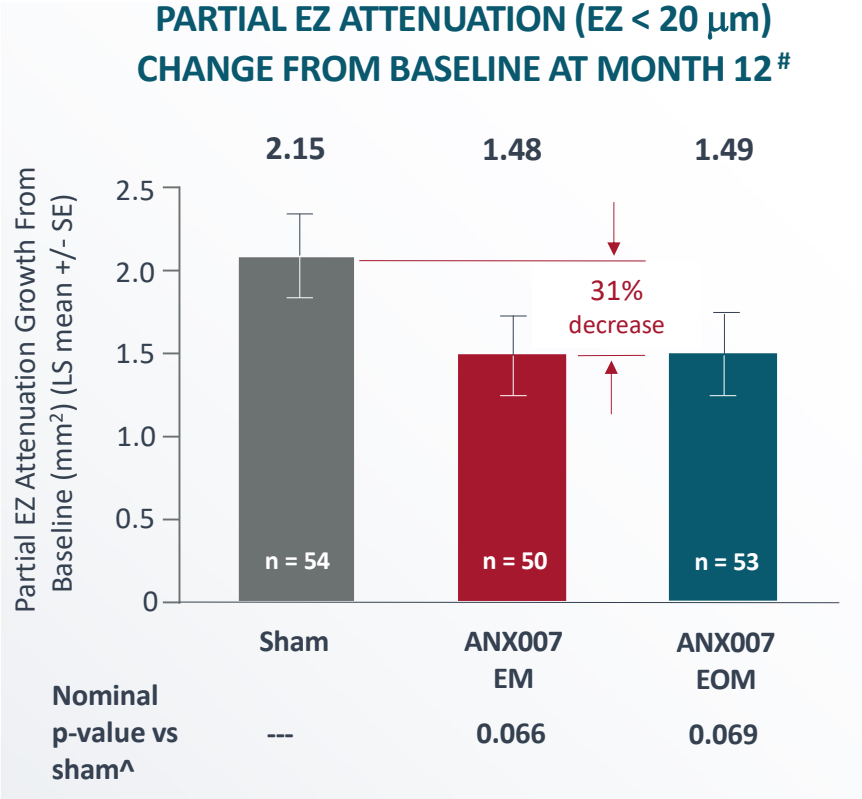
	Sham	ANX007 EM	ANX007 EOM
Nominal p-value vs sham^	---	0.0008	0.0363

#Persistent for two consecutive visits through month 12 or at last visit
^Nominal p-value from a Chi-square test in EZ population (n = 194)
** Nominal p < 0.05*

Initial Assessment of Ellipsoid Zone Change: ANX007 Demonstrated ~30% Change from Sham in EZ Attenuation

As observed 12-month completer data; MMRM analysis ongoing, pending full timepoint assessment





#Data as observed
^Nominal p-value from a linear regression with Heidelberg Spectralis OCT population with baseline and month 12 EZ data (n = 157)
** Nominal P < 0.05*

ANX007 Generally Well-Tolerated

ADVERSE EVENTS OF SPECIAL INTEREST n (%)	SHAM (N=89)	ANX007 EM (N=89)	ANX007 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 – No Cases Reported			
Intraocular Inflammation+	0	2 (2.2%)	1 (1.1%)
Ischemic Optic Neuropathy+ - No Cases Reported			

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

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

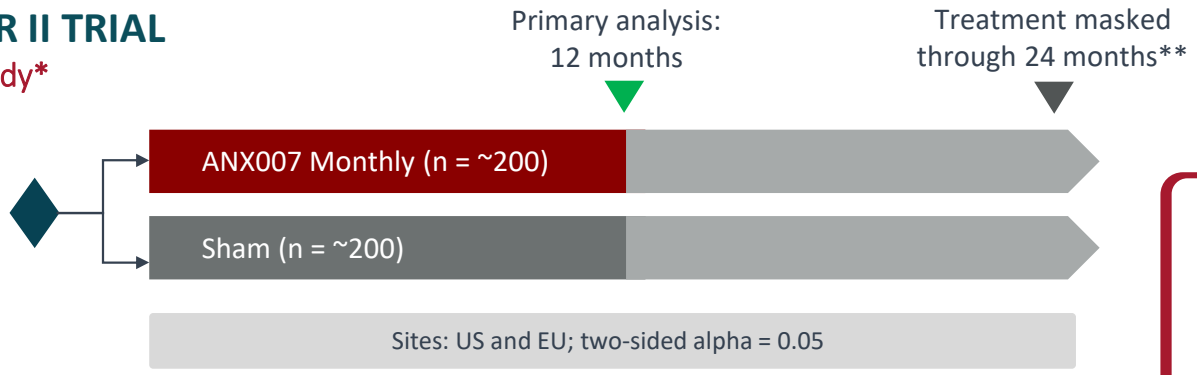
*Event Verbatim term listed

ANX007 Global GA Pivotal Program to begin Mid-2024

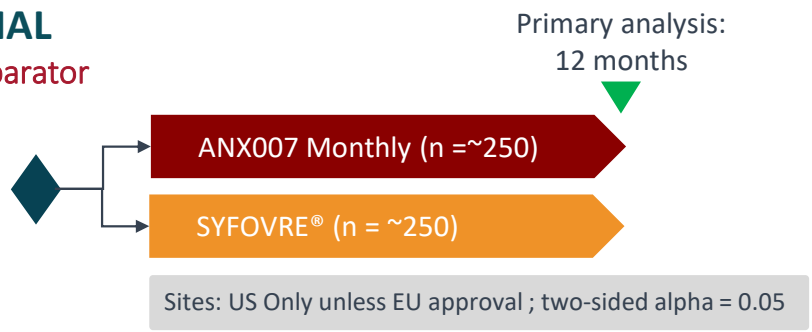
Replicate ARCHER and support global approvals

PRIME Designation from EMA

ARCHER II TRIAL
Sham Study*



ARROW TRIAL
Injection Comparator



Primary Endpoint
Persistent ≥15-Letter BCVA Loss through 12 months, or accumulation of appropriate number of events – Aligned with FDA

Key Secondary Endpoints
Safety, Low Luminance VA (LLVA), Low Luminance Visual Deficit (LLVD)

*ARCHER n=270 GA patients. **24 months total treatment per regulatory direction

ANX007: A Novel Neuroprotective Agent Demonstrating Benefit in Vision in ARCHER Trial

- **ANX007's unique mechanism of action targets C1q pathway to protect photoreceptors**
- **ANX007 demonstrated consistent visual function benefits**
  - Highly statistically significant on visual acuity endpoint
  - Dose and time dependent
  - Benefit in foveal and non-foveal patients
- **Initial EZ assessment showed ~30% slowing of photoreceptor loss at 12 months**
- **Generally well tolerated**
- **ANX007 global Phase 3 program is under development with first and only EMA PRIME designation in GA**