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

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Disclosures

- Dr. Heier is a consultant for 4DMT, Abpro, Adverum, Affamed, AGTC, Akouos, Alzheon, **Annexon**, Apellis, Asclepix, Aviceda, B&L, Biovisics, Boehringer Ingleheim, Curacle, Daiichi Sankyo, Exegenesis, Genentech/Roche, Glaukos, Gyroscope, Immunogen, IvericBio, Janssen R&D, jCyte, Kriya, Nanoscope, NGM, Notal, Novartis, Ocular Therapeutix, Ocuphire, OcuTerra, OliX, ONL Therapeutics, Outlook TX, Perceive Biotx, Ray Tx, Regeneron, Regenxbio, RetinAI, Sanofi, Stealth Biotx, Thea, Unity Bio and Vanotech.
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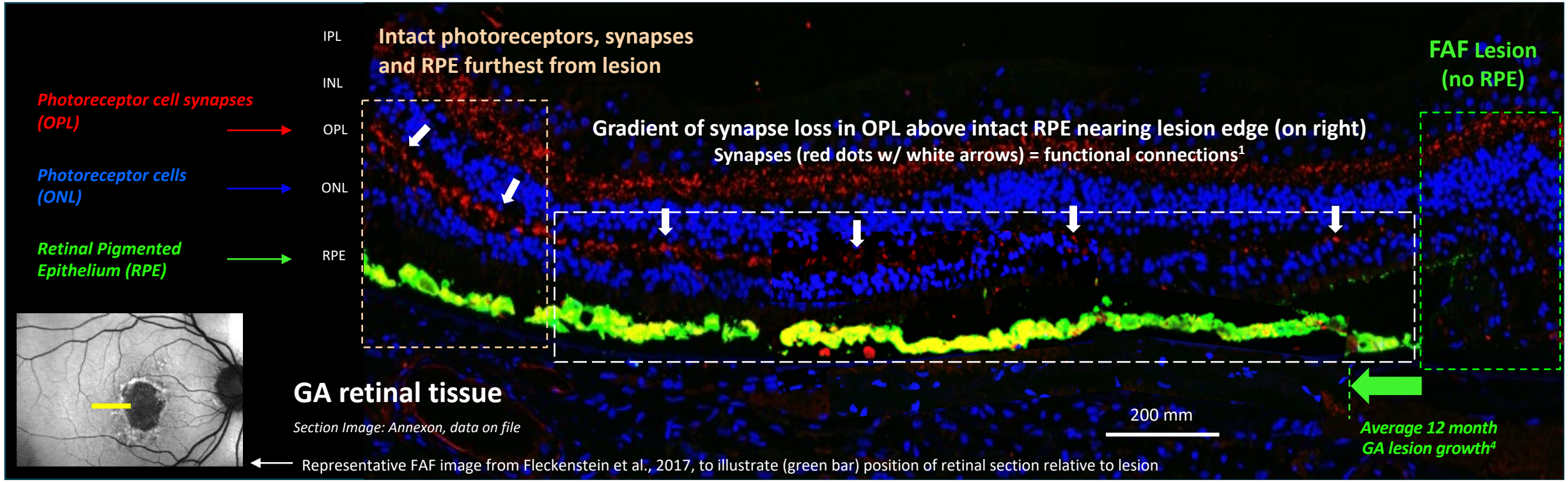
- Dr. Heier is a member of the Board of Directors of Ocular Therapeutix.
- Dr. Heier holds equity in Adverum, Aldeyra, Allegro, Aviceda, DTx Pharma, jCyte, Ocuphire, Ocular Therapeutix, RevOpsis, Vinci, and Vitranu.
- Study funded by Annexon Biosciences.

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

- Photoreceptor cells and their synapses are lost over intact RPE (white box)
  - Decreasing gradient of red-labeled photoreceptor synapses moving toward the lesion on right - loss of synapses is loss of function[1]
  - Also, decreasing gradient of blue-labeled photoreceptor cells toward lesion – photoreceptors are lost prior to RPE[2]
- FAF measures RPE loss/lesion growth, but not photoreceptor or synapse / cell loss and correlates poorly w/ visual function[3]

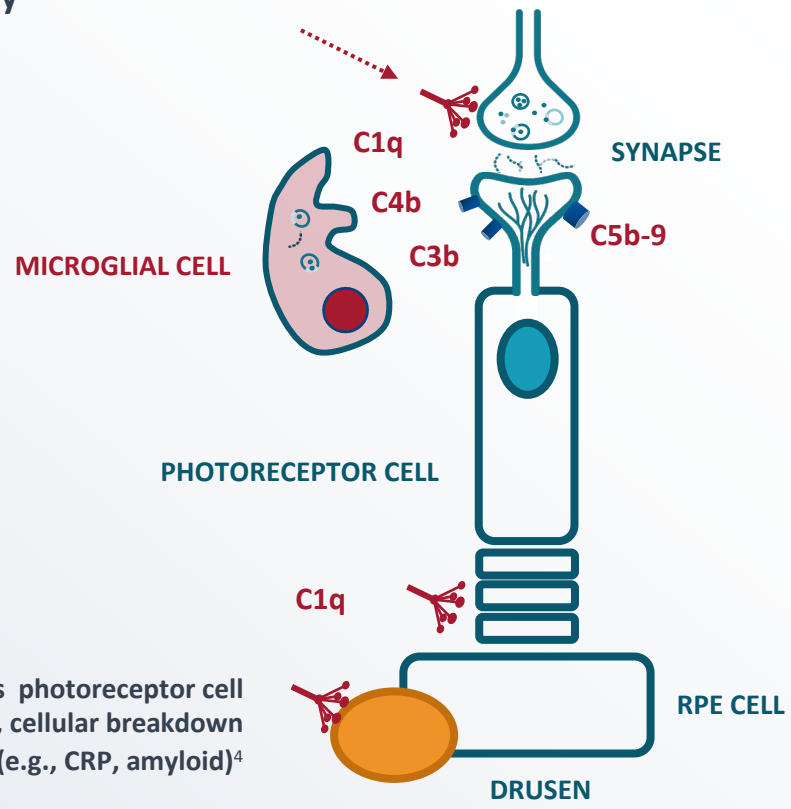


[1]Selkoe, 2002 doi: 10.1126/science.1074069; Burger, et al., doi.org/10.1016/j.ydbio.2021.04.001; [2]Bird et al., 2014 *JAMA Ophthalmol* doi:10.1001/jamaophthalmol.2013.5799; Li, et al., 2018 *Retina* 38:1937; Pfau, et al., 2020 10.1001/jamaophthalmol.2020.2914; Sarks, et al., 1988 *Eye* 2:552; [3]Heier,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

Anti-C1q: A Distinct Neuroprotective Mechanism

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

C1q binds stressed photoreceptor synapses and activates the classical pathway



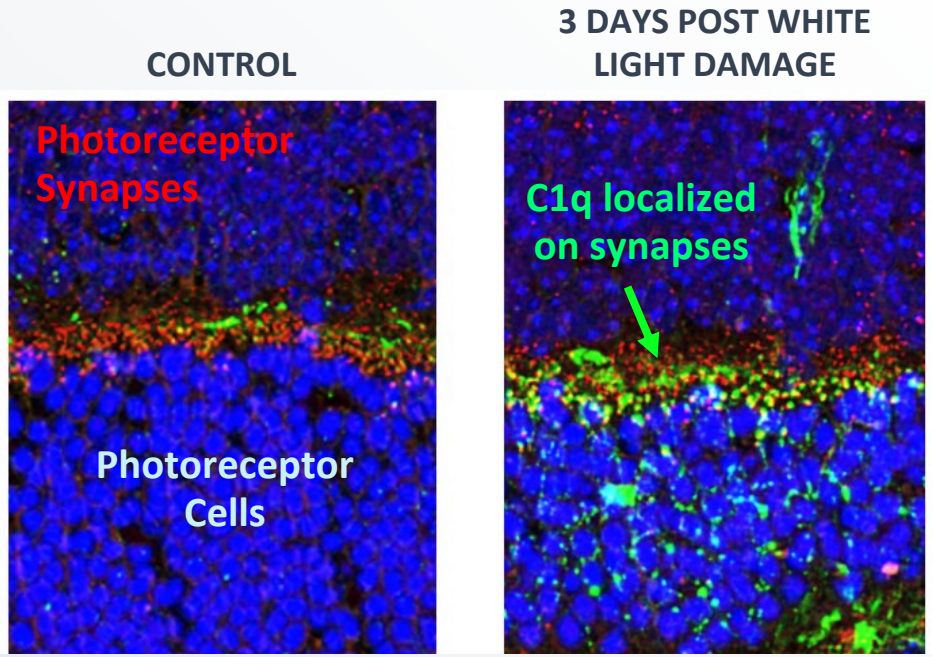
In GA, **C1q** also binds photoreceptor cell outer segments, cellular breakdown products and drusen (e.g., CRP, amyloid)[4]

- 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]

[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

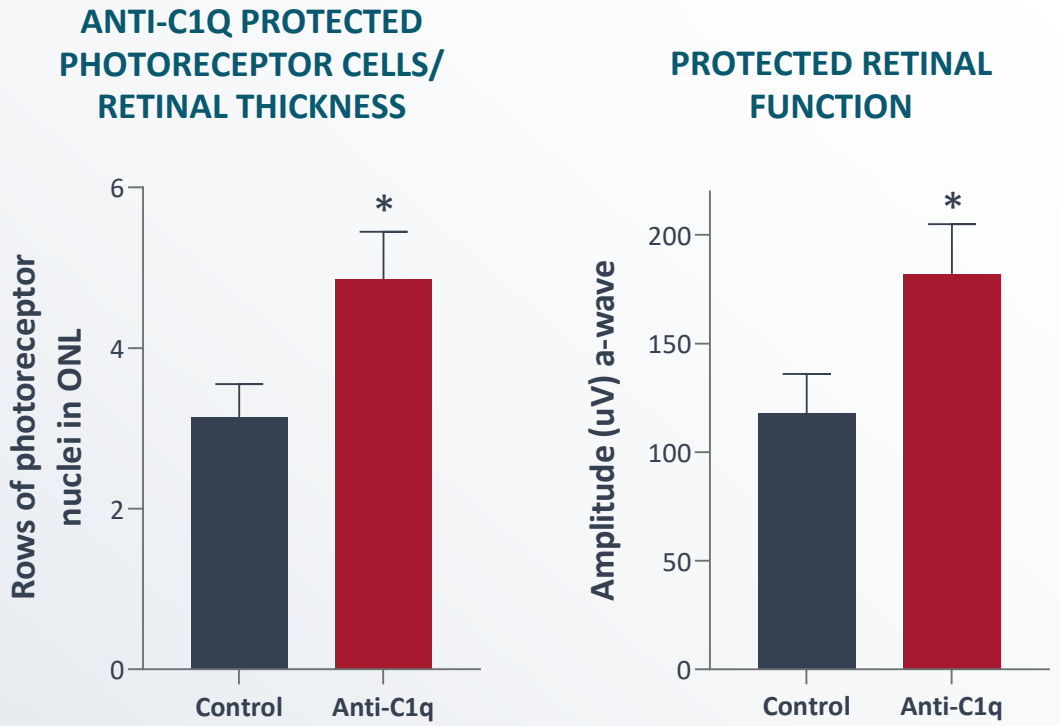
Anti-C1q Protected Photoreceptor Cells and Their Function in Models of Photoreceptor Damage

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



Annexon data on file

Anti-C1q Protected Photoreceptors and Function



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

ANX007: Differentiated Inhibitor of C1q and Classical Complement to Treat Geographic Atrophy

ANX007

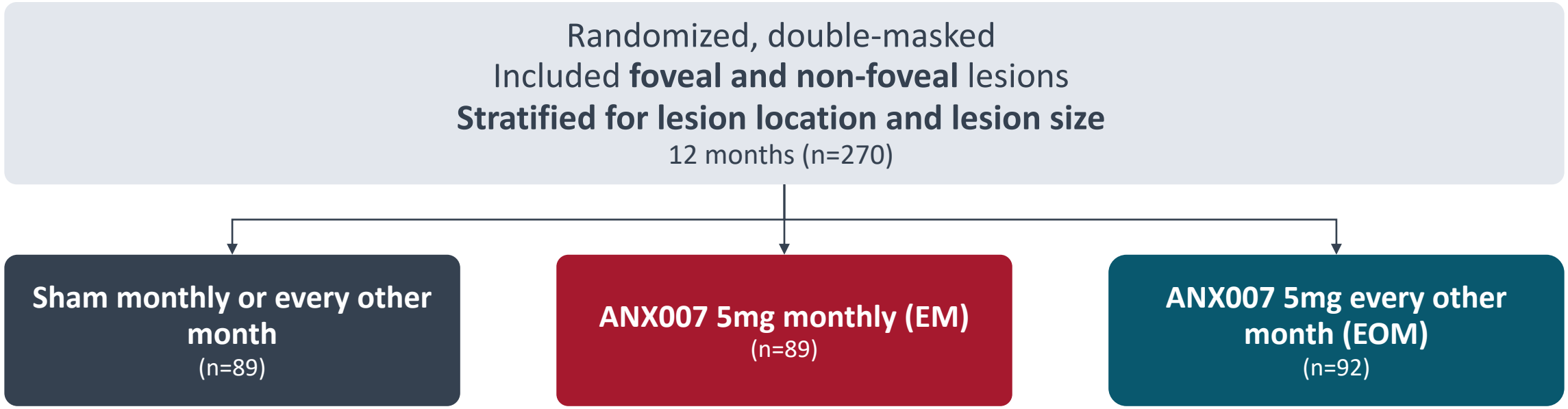
IVT administered antigen-binding fragment (Fab)

KEY ATTRIBUTES

- ✓ **Design:** Modeled after established IVT administered Fab antibodies
- ✓ **Profile:** 50kD Fab antibody; low viscosity / non-pegylated; <10 pM potency formulated for intravitreal administration
- ✓ **Dosing:** 5 mg / 100 microliter. PK in patient aqueous humor supports monthly/every other month dosing
- ✓ **Specificity:** Full target engagement / inhibition of classical complement pathway observed; lectin and alternative pathway in place for immune and homeostatic functions[1]

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

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



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

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

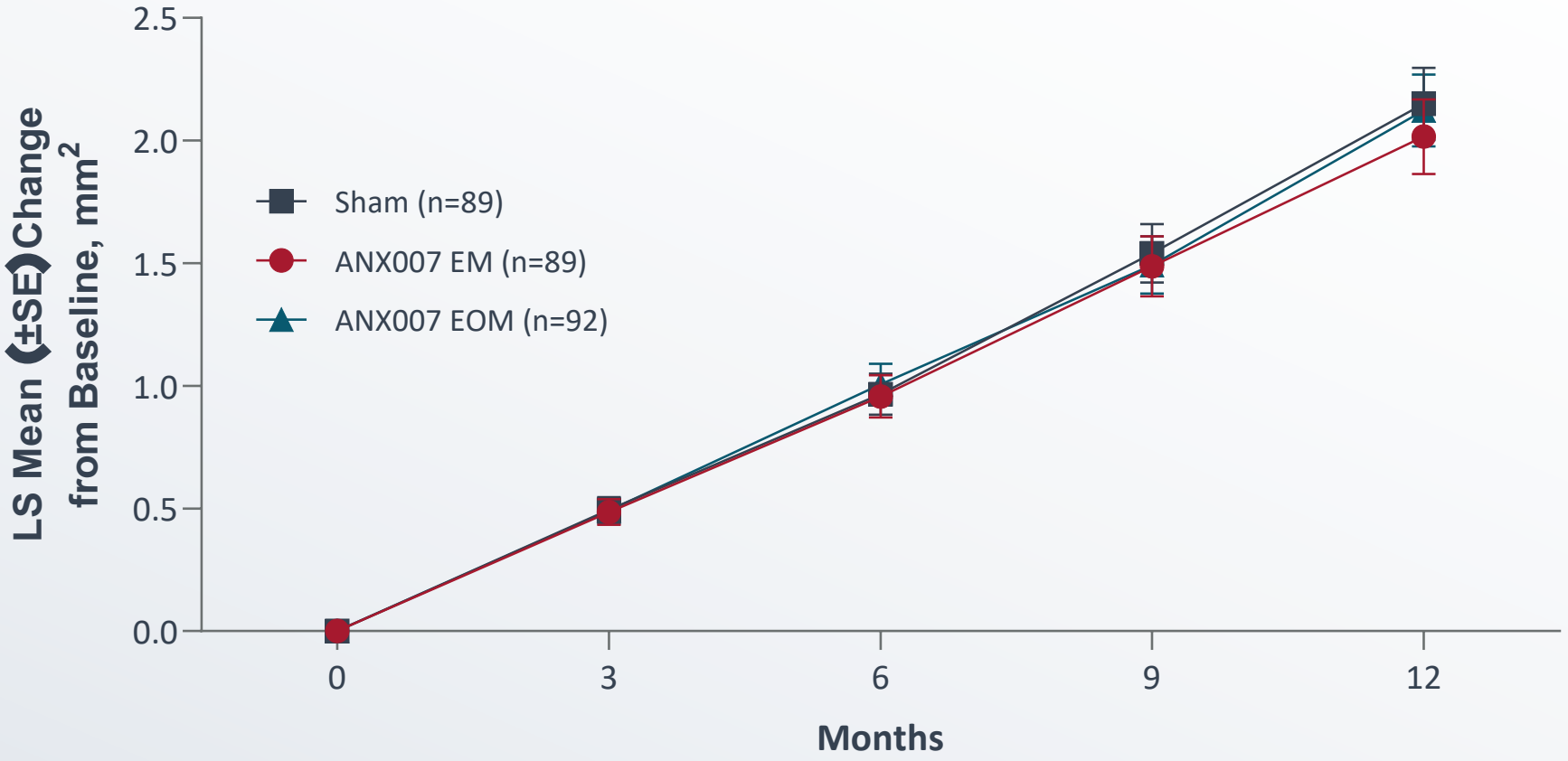
CHARACTERISTIC	SHAM POOLED (N=89)	ANX007 EM (N=89)	ANX007 EOM (N=92)
Age, mean (SD)	79.8 (7.49)	79.7 (8.64)	80.5 (8.53)
Female, n (%)	59 (66.3%)	47 (52.8%)	60 (65.2%)
Caucasian, n (%)	87 (97.8%)	87 (97.8%)	89 (96.7%)
Mean BCVA, mean (SD)	**58.5 (16.2)**	**58.8 (17.2)**	**58.3 (15.0)**
Foveal Lesion	49.4%	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%)

Discontinuations Consistent with Previous GA Studies

	SHAM (N=89)	EM (N=89)	EOM (N=92)
Discontinued treatment	**10 (11.2%)**	**13 (14.6%)**	**11 (12.0%)**
Withdrawal by subject			
Unrelated health issues	2	1	2
Moved / travel / time	1	2	2
Personal reasons / no reason given	2	3	2
Other	1	2	---
Death	2	2	3
Lost to follow-up	1	2	2
Physician decision	1	1	---

ANX007 Did Not Significantly Reduce Lesion Area, a Surrogate Biomarker of Functional Change in GA

GA LESION AREA CHANGE FROM BASELINE TO MONTH 12+



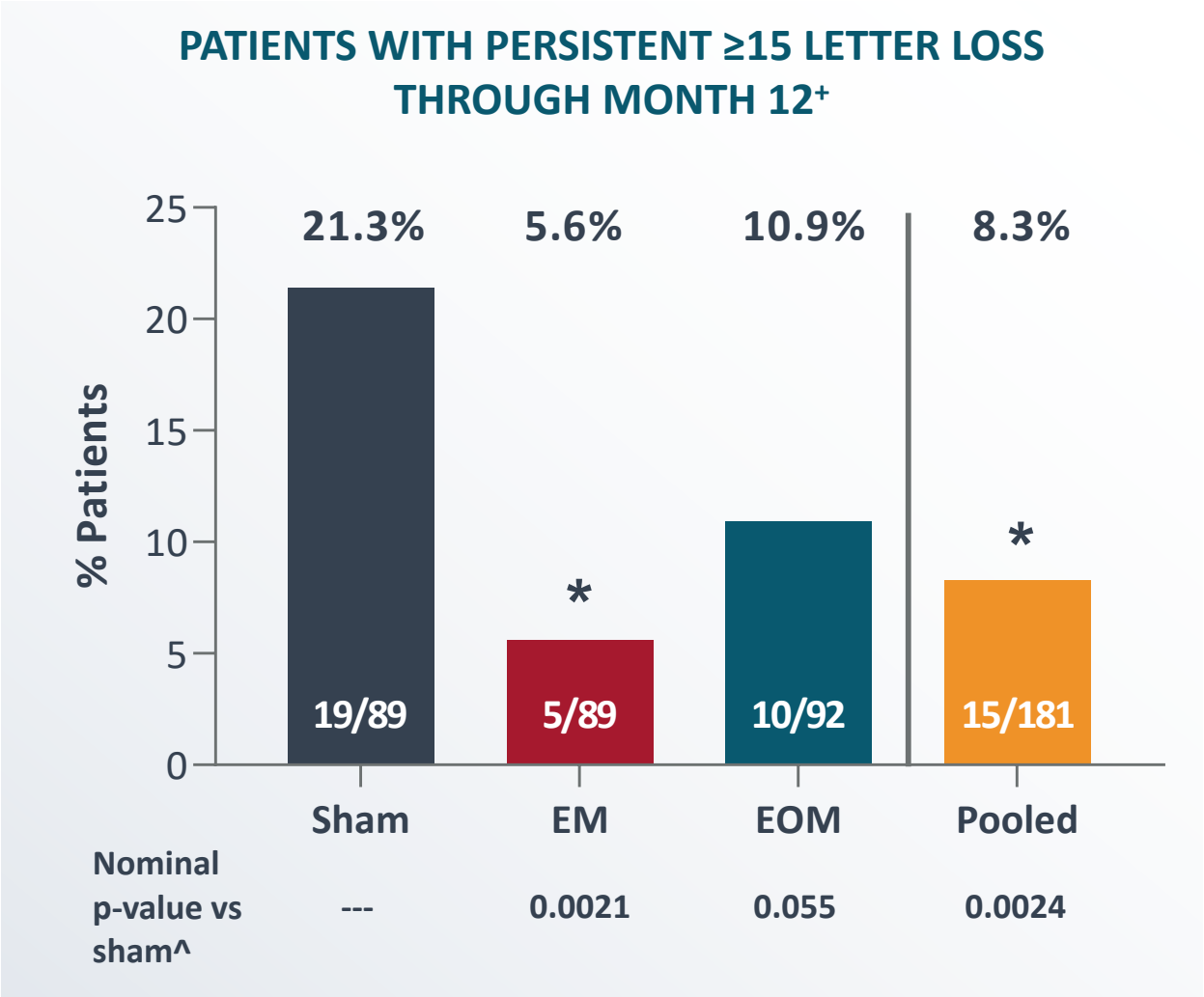
GA Area Change from Baseline at 12 Month

Arm	mm²	%	p-value
Sham	2.15	---	---
EM^	2.02	-6.2%	0.526
EOM^	2.12	-1.3%	0.896

^2-arm MMRM model

+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.

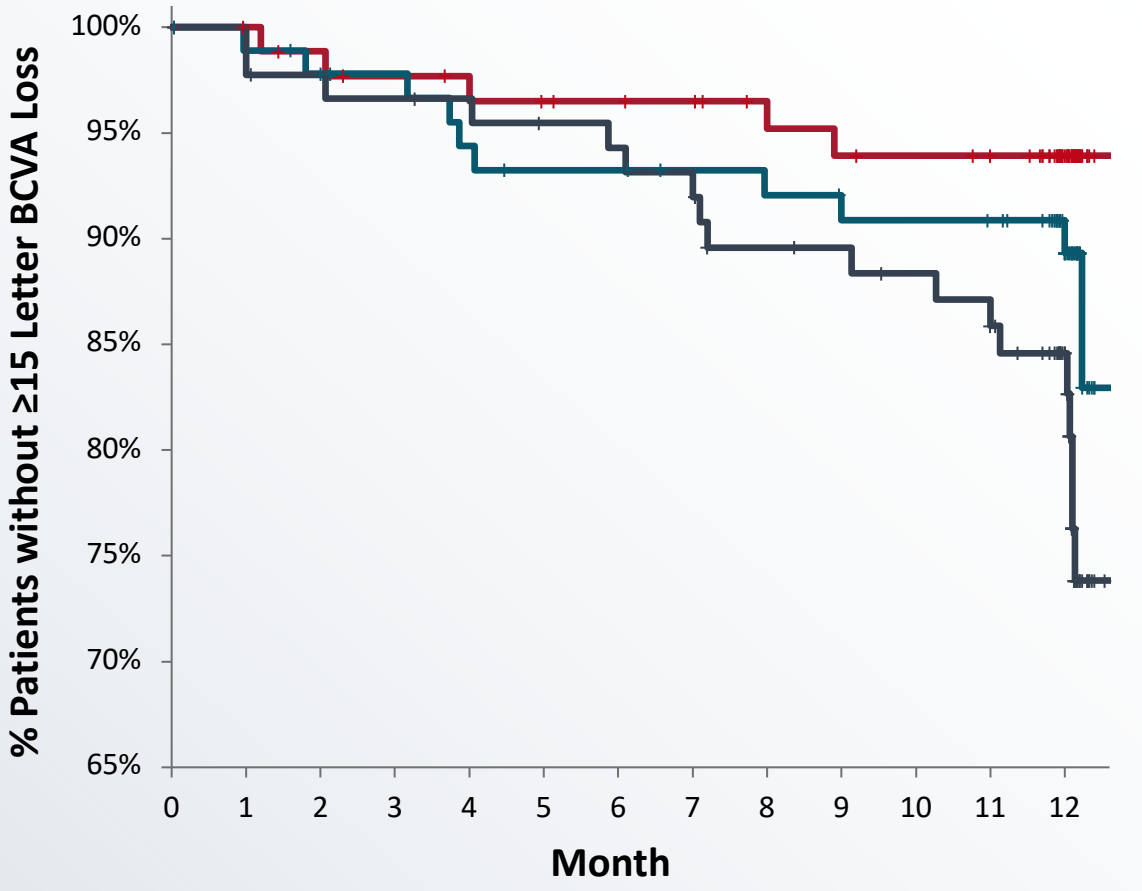
Prespecified Secondary Endpoint (BCVA): ANX007 Demonstrated Significant, Dose-Dependent Protection From Vision Loss



- Dose-dependent response
- 15 letter loss clinically meaningful
- Widely-accepted endpoint

+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

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

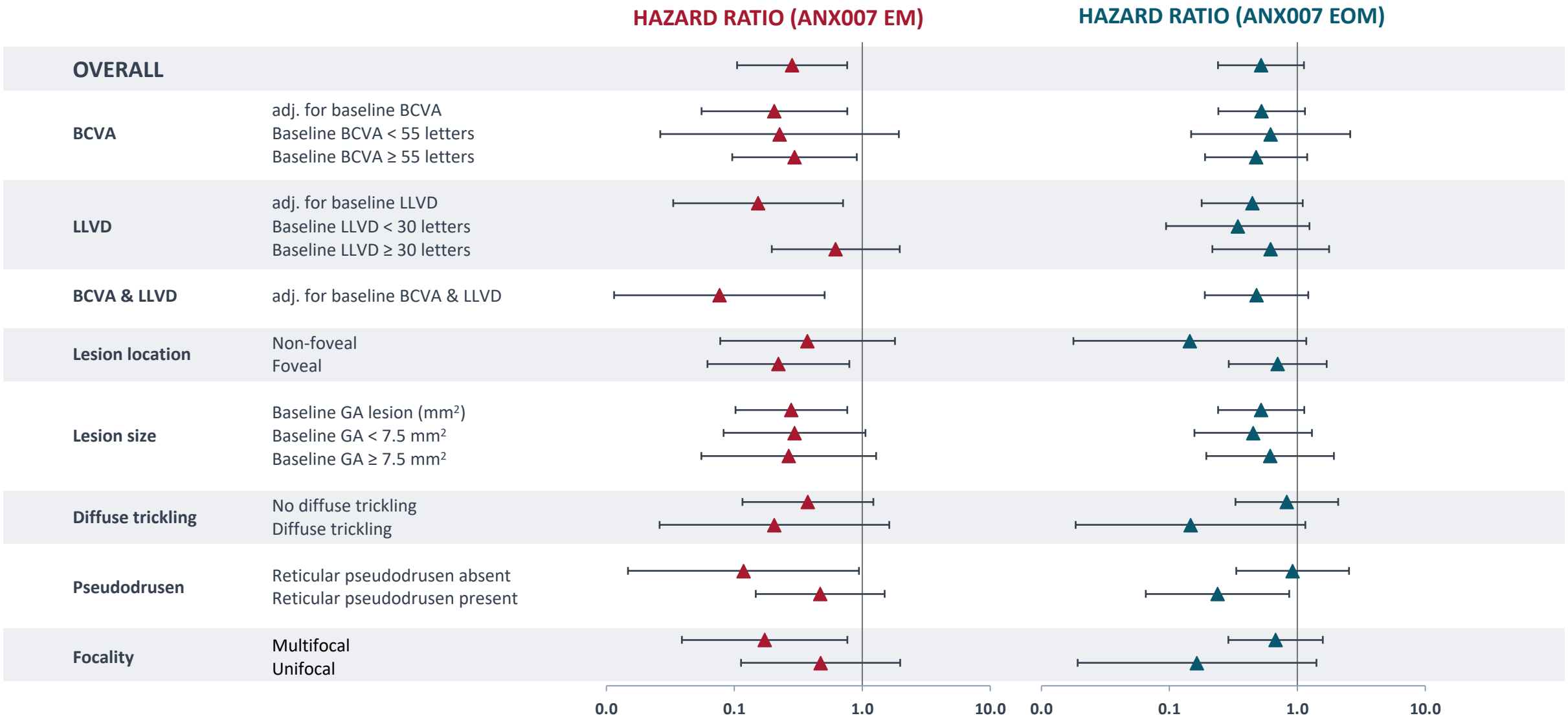
Sham (n=89)

Sensitivity analysis confirmed treatment effect:

Significant 66% reduction in risk in EM group when excluding patients with vision loss only at month 12

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

ANX007 Protection from Vision Loss Consistent Across Baseline Characteristics

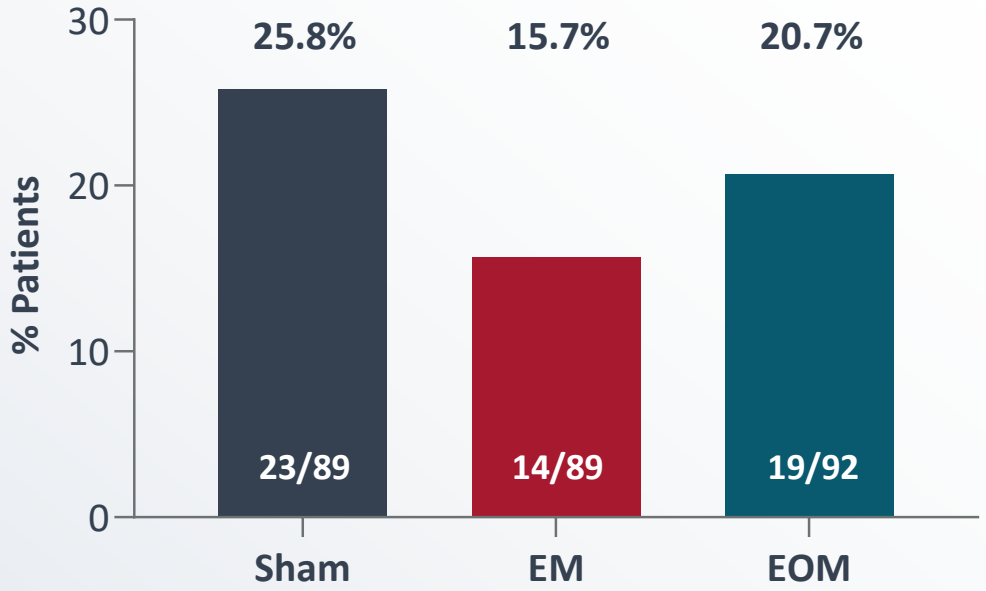


*persistent for two consecutive visits through month 12 or at last visit; Hazard ratios are from Cox regressions accounting for event time and censorship
NOTE: Hazard ratio not estimated for ANX007 EM vs Sham with baseline LLVD < 30 due to zero (0) event in ANX007 EM group for the subgroup.

Consistent Protection from Vision Loss with BCVA ≥10 and ≥20 Letter Assessments

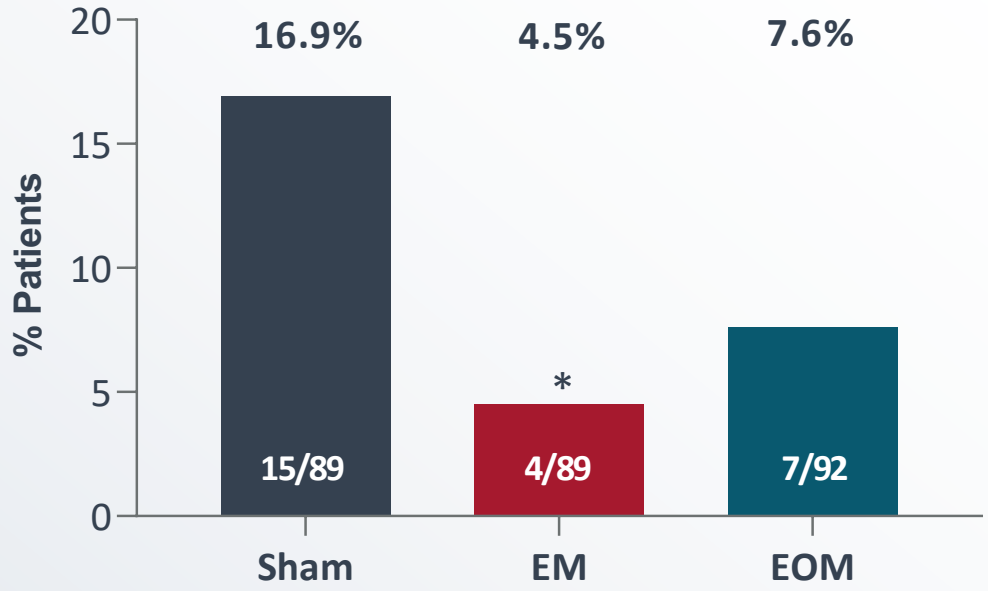
Persistent BCVA Vison Loss Through Month 12[+]

≥10 LETTER LOSS



Nominal p-value vs sham^	---	0.096	0.408

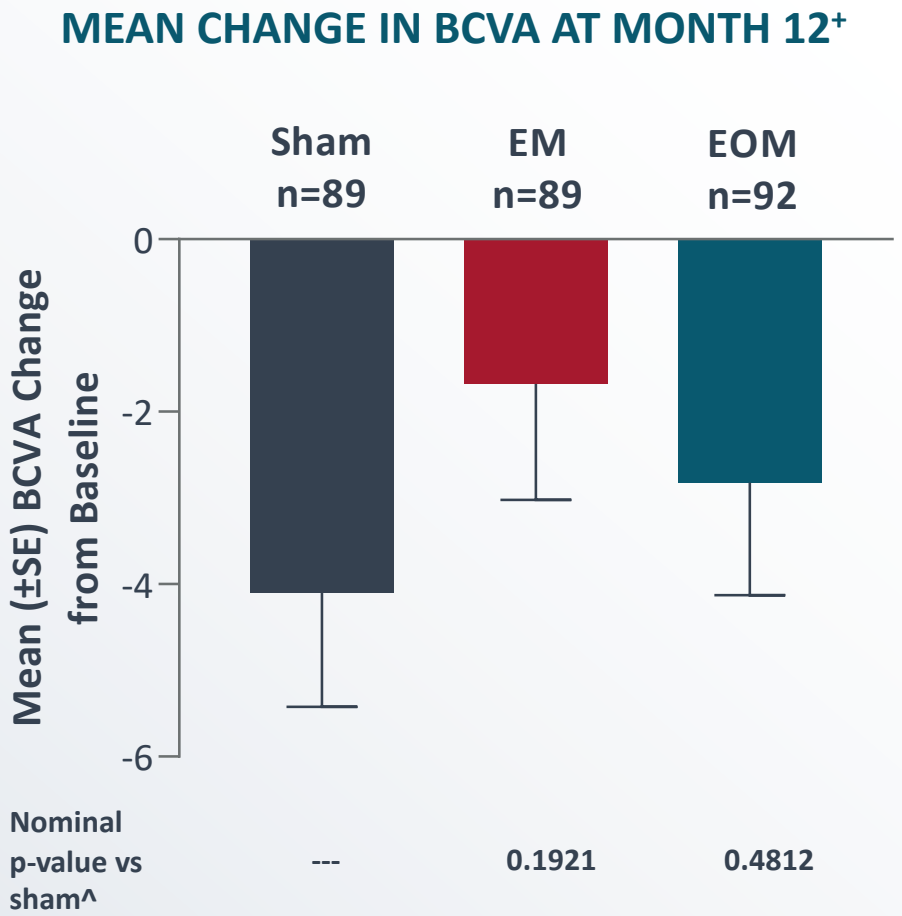
≥20 LETTER LOSS



Nominal p-value vs sham^	---	0.0076	0.57

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

Mean Change in BCVA at Month 12 Further Supports Consistent Protection From Vision Loss with ANX007 Treatment



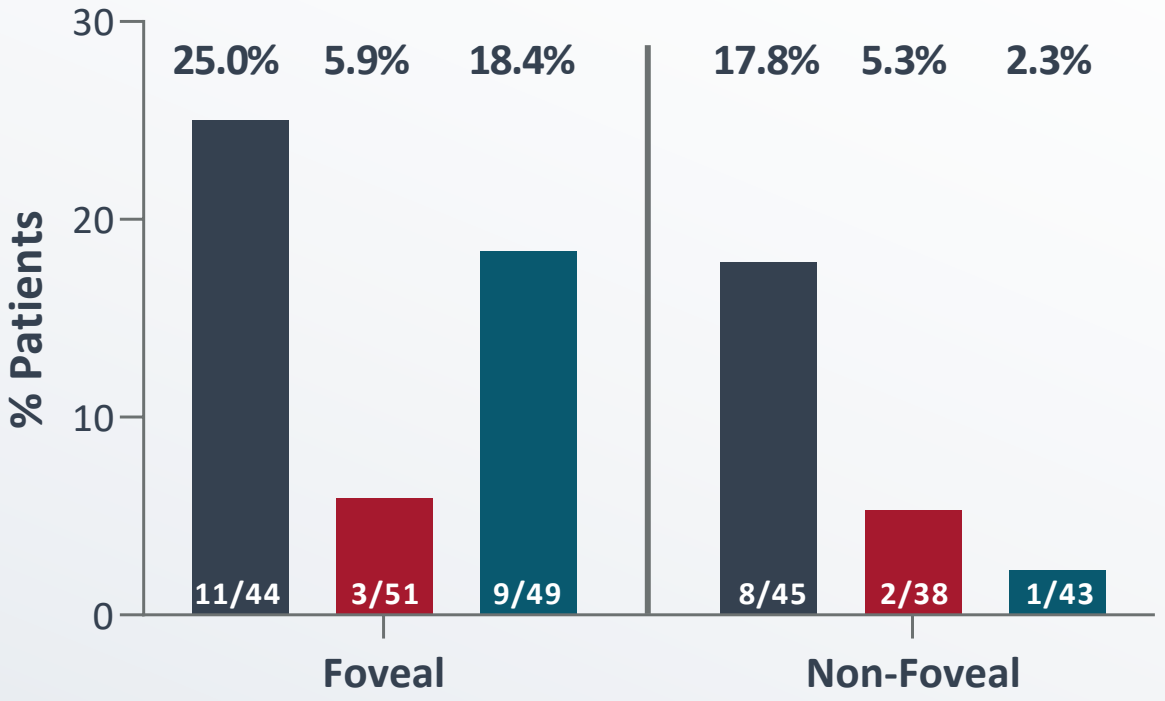
- Trend for dose-dependent response in ANX007 treated groups
- BCVA loss in sham through 12 months consistent with previous GA trials[1,2,3,4]

+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 MMRM adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction in ITT population

[1]Liao et al (2020) *Ophthalmology* 127: 186-195; [2]Holtz et al (2018) *JAMA Ophthalmology* 136:666-677;
[3]Jaffee et al (2021) *Ophthalmology* 128:576-586; [4]Heier et al, *Retina Society* 2022

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

PATIENTS WITH PERSISTENT ≥15 LETTER LOSS THROUGH MONTH 12+



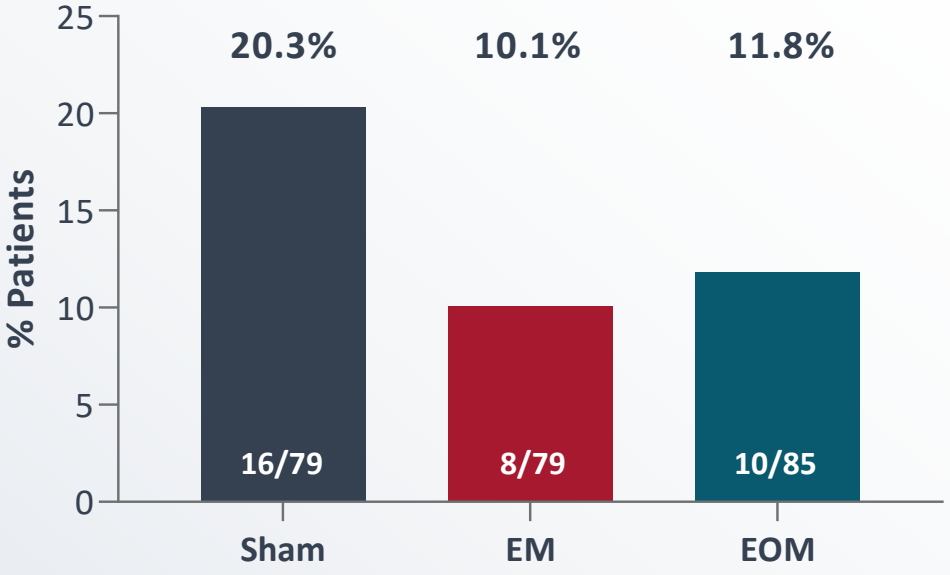
Nominal summary p-value vs. sham^	
EM	0.0019
EOM	0.0439

+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

Prespecified Secondary Analyses: ANX007 Provided Consistent Protection from Vision Loss on Additional Measures—LLVA & LLVD

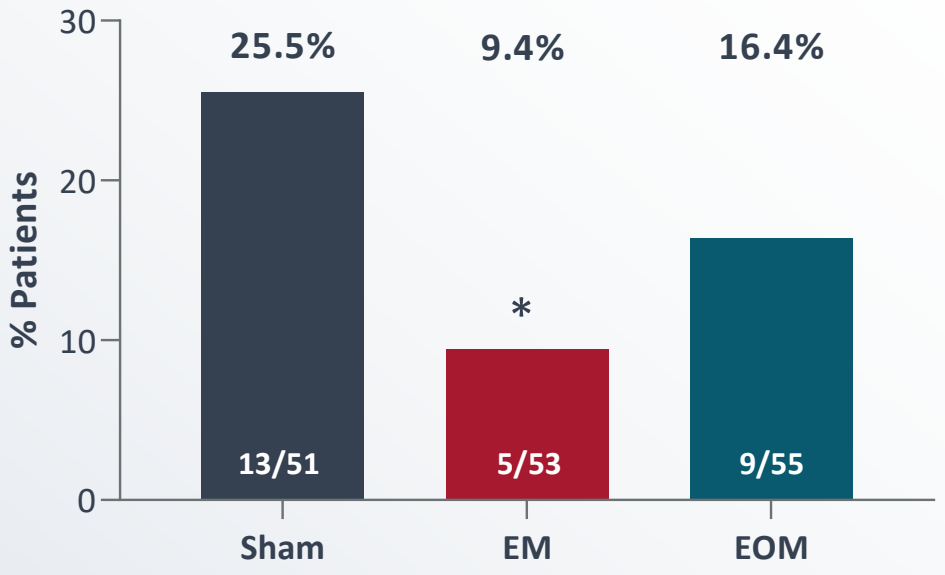
LLVA ≥15 LETTER LOSS THROUGH MONTH 12+^



	Sham	EM	EOM
Nominal p-value vs Sham^	--	0.076	0.14

+Patients with at least one post baseline LLVA measurement
^Nominal p-value from a Chi-square test

LLVD ≥15 LETTER WORSENING THROUGH MONTH 12+^



	Sham	EM	EOM
Nominal p-value vs sham^	--	0.0305	0.2470

+in subjects with BCVA ≥55
^Nominal p-value from a Chi Square test
*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	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; reviewed by DSMC and reading center (masked)
+Not AESI, included because of current interest

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

- **C1q inhibition: distinct neuroprotective MOA**
- **Consistent demonstration of visual function benefits**
  - Highly statistically significant on visual acuity endpoint
  - Dose and time dependent
  - Consistent across multiple prespecified measures of BCVA (10, 15, 20 letter loss)
  - Benefit in foveal and non-foveal patients
  - Benefit in additional prespecified measures of visual function (LLVA, LLVD)
- **A significant change in lesion area growth not seen through 12 months**
- **Generally well tolerated**
- **6 month follow up ongoing**
- **Planning for regulatory discussions and Phase 3**