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

David Lally, Jeffrey Heier, Charles Wykoff, Glenn Jaffe, Roger A. Goldberg, Allen Hu, Carl Regillo, David Boyer, Karl Csaky, Wendy Murahashi, Harman Hansra, Scott Borland, Lori Taylor and Donald Fong

for the ARCHER Investigators

Disclosures

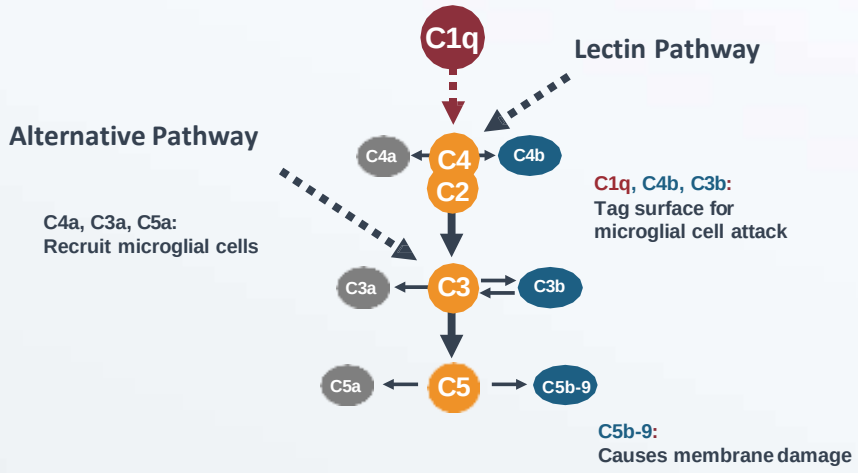
- Financial disclosures:
  - Affamed (research grants), AGTC (consultant), Aldeyra Therapeutics (research grants), Alexion (research grants), Alimera (consultant), Allergan (speaker), **Annexon** (consultant; research grants), Apellis (consultant; research grants), Boehringer Ingelheim (consultant), Curacle (consultant; research grants), Emmes/LMRI (research grants), Eyebio (research grants), EyePoint (consultant; research grants), Delsitech (speaker), Genentech/Roche (consultant; research grants; speaker), Iveric Bio (consultant; research grants), Kodiak (research grants), Laboratories Thea (consultant), Neurotech (consultant; research grants), Notal Vision (consultant), Novartis (consultant, research grants), Ocuphire (consultant; equity options; research grants), Opthea (consultant; research grants), Outlook Therapeutics (consultant), Oxurion (research grants), Pykus Therapeutics (research grants), Regeneron (consultant; speaker), Stealth Biotherapeutics (consultant; research grants), Xequel Bio (consultant)

- Study funded by Annexon Biosciences

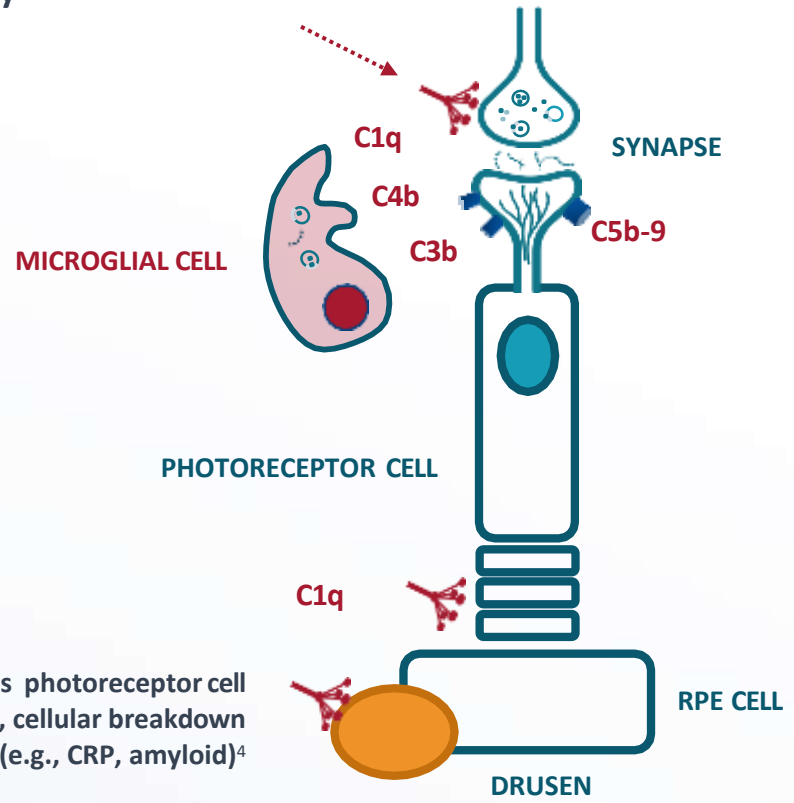
Anti-C1q: A Distinct Neuroprotective Mechanism

C1q initiates classical complement cascade to drive photoreceptor synapse & 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]

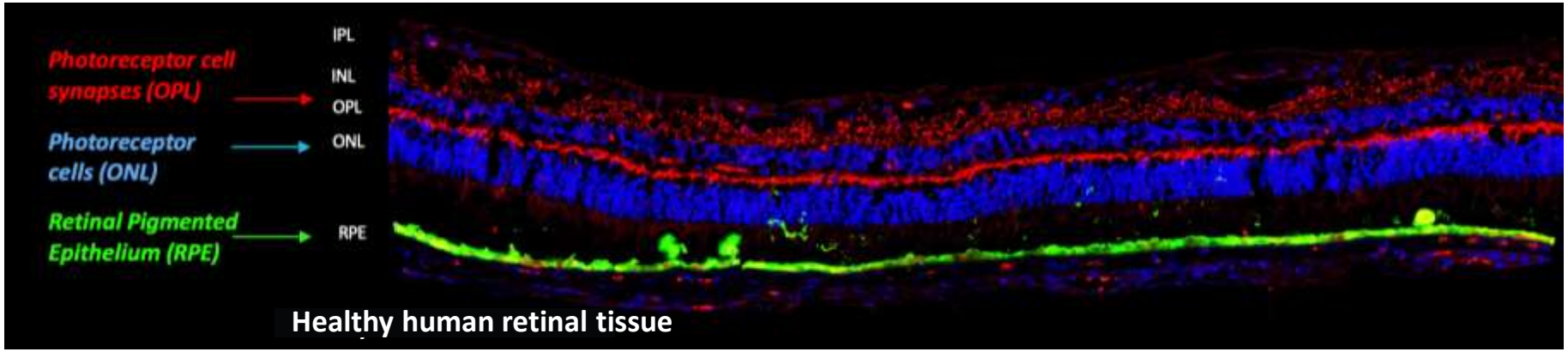
[1]Stevens, 2007, *Cell* **131**:1164; Howell, et al., 2011 *J Clin Invest*. **121**:1429; Schafer, et al., 2012 *Neuron* **74**: 691; Stephan et al., 2012 *Annu Rev Neurosci* **35**:369; Hong, et al., 2016 *Science*. **352**:712; Lui, et al., 2016 *Cell* **165**:921; Dejanovic, et al., 2018 *Neuron* **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

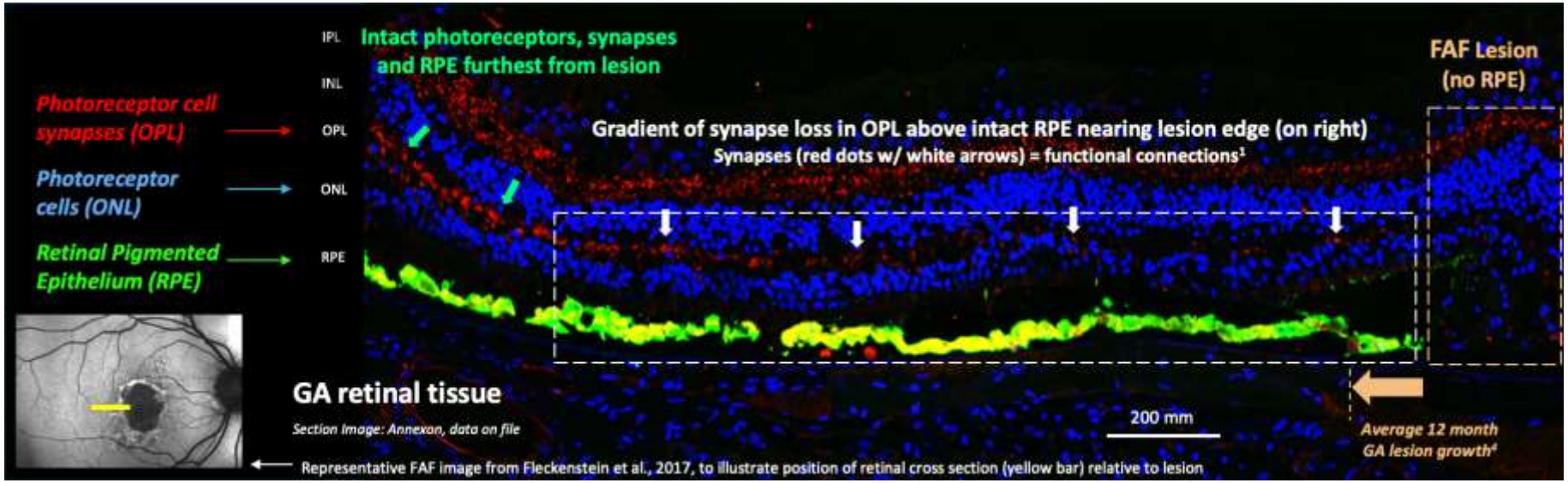
Healthy Human Retina (top)

- 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;

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

FDA Fast Track status and EMA PRIME Designation granted for ANX007

ANX007

IVT administered antigen-binding fragment (Fab)

KEY ATTRIBUTES

- ✓ **Design:** Constant region framework 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; lectin and alternative pathways 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

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

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+

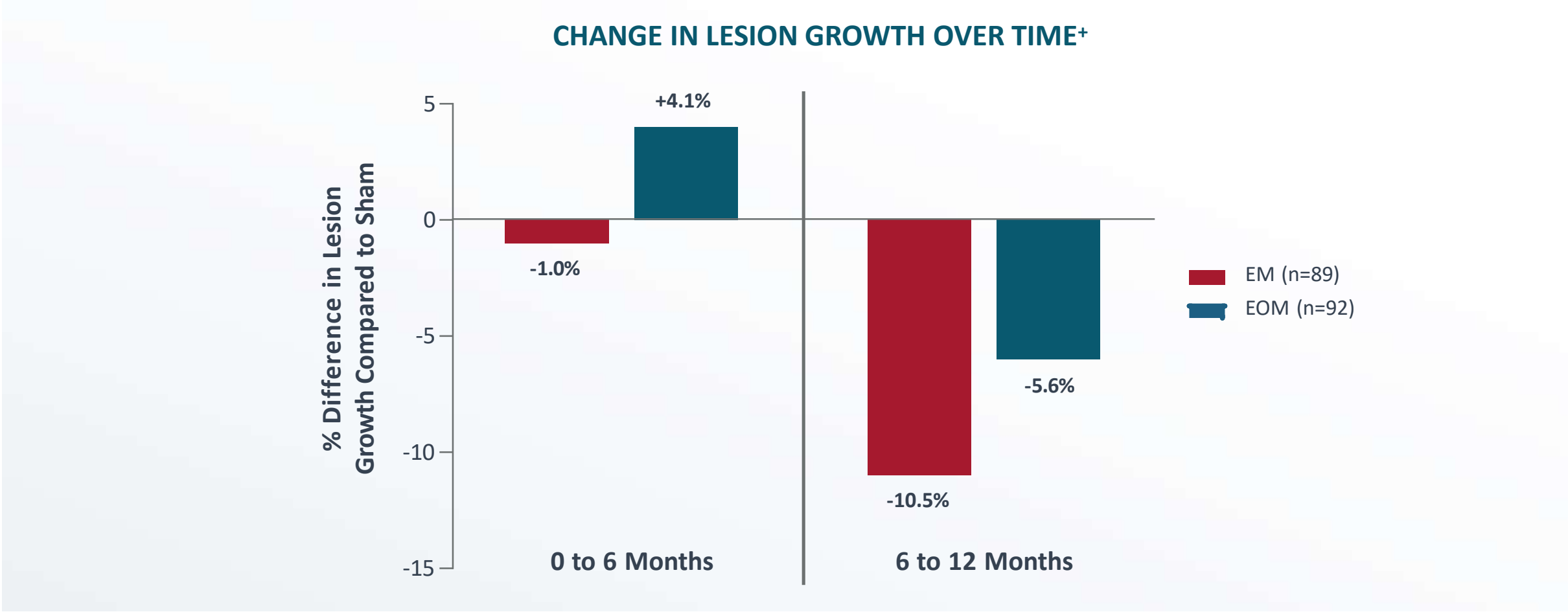
GA Area Change from Baseline at 12 Months

Arm	mm^2	%	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.

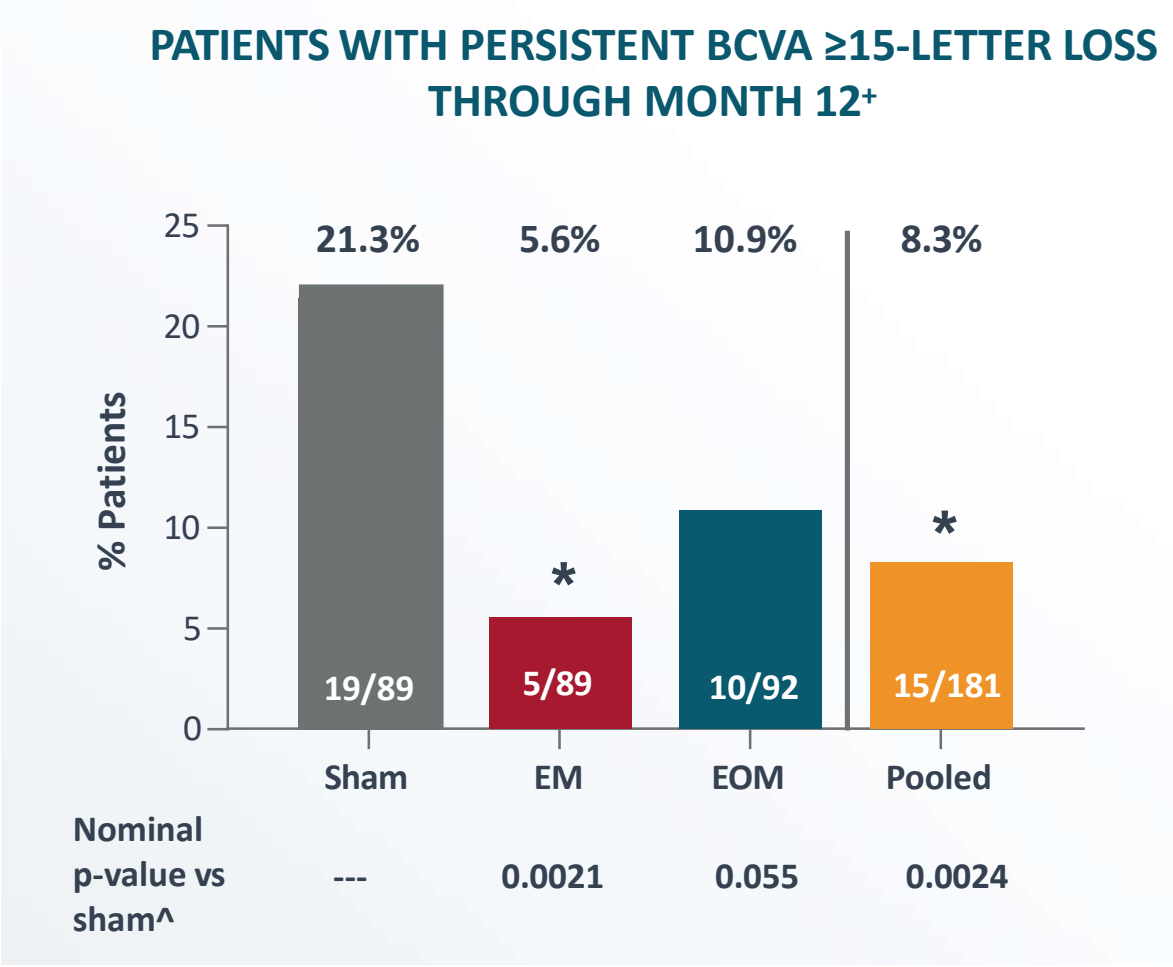
ANX007 Effect on Lesion Growth Improves with Longer Treatment



+The 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

Increasing ANX007 Impact Over Time

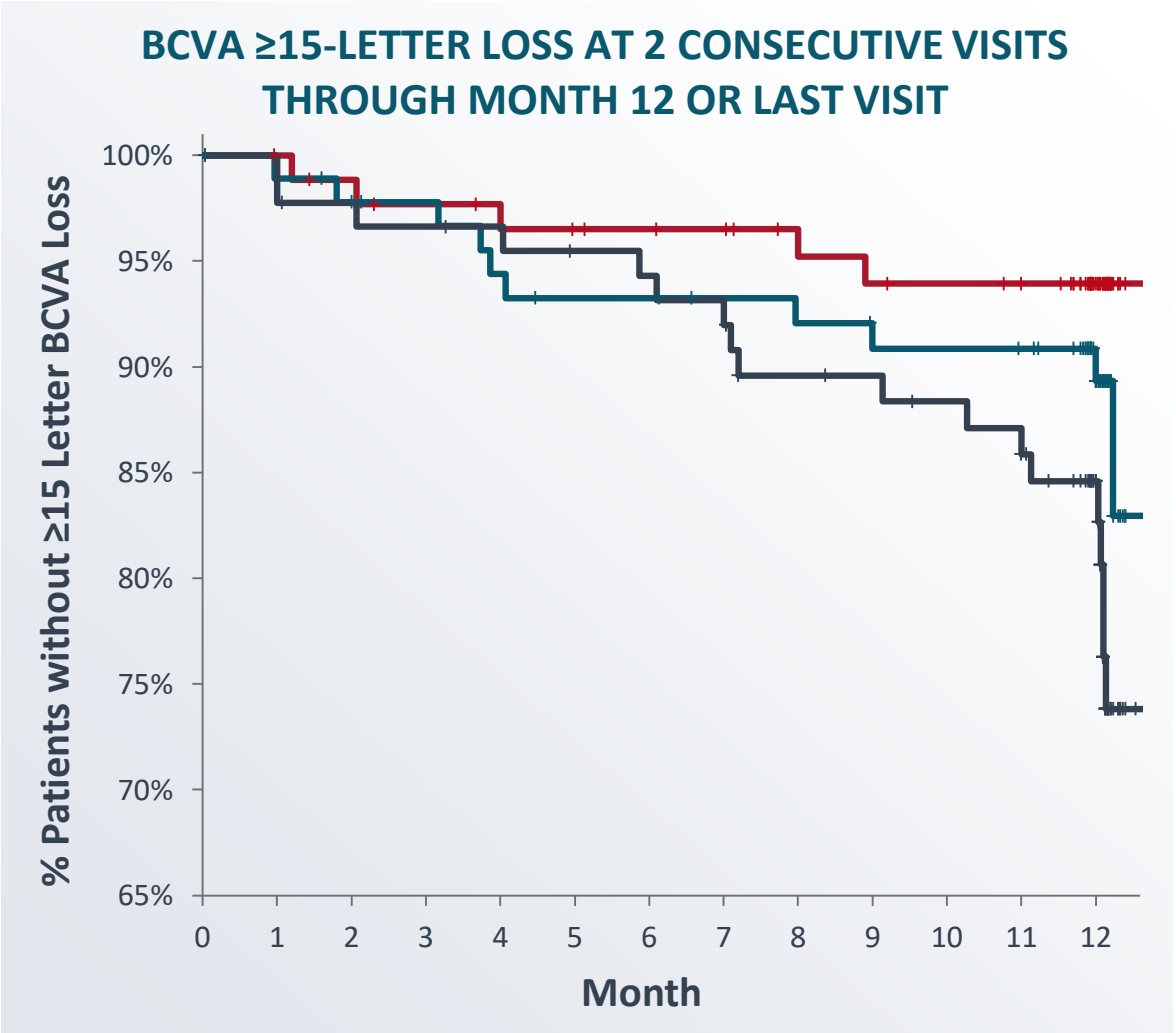
ANX007 Demonstrated Statistically Significant Protection From Vision Loss as Measured by BCVA ≥15-Letter Loss



+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 BCVA ≥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:

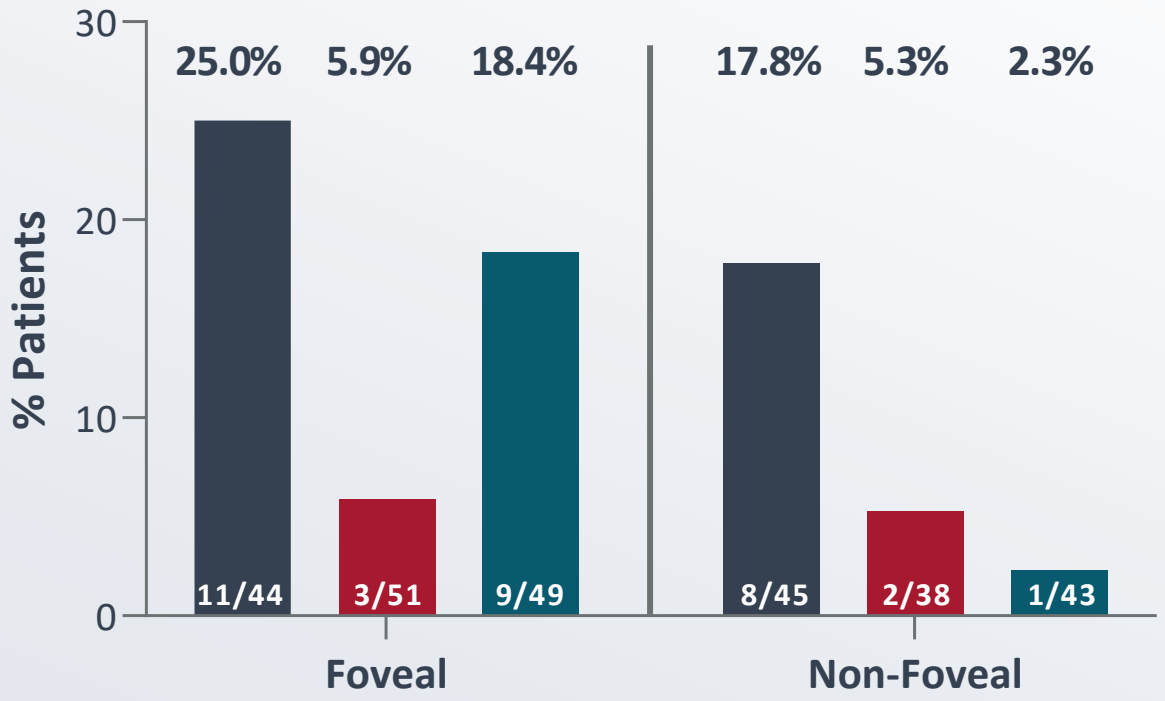
Significant 66% reduction in risk in EM group when excluding patients with vision loss only at month 12

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

Increasing ANX007 Impact Over Time

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

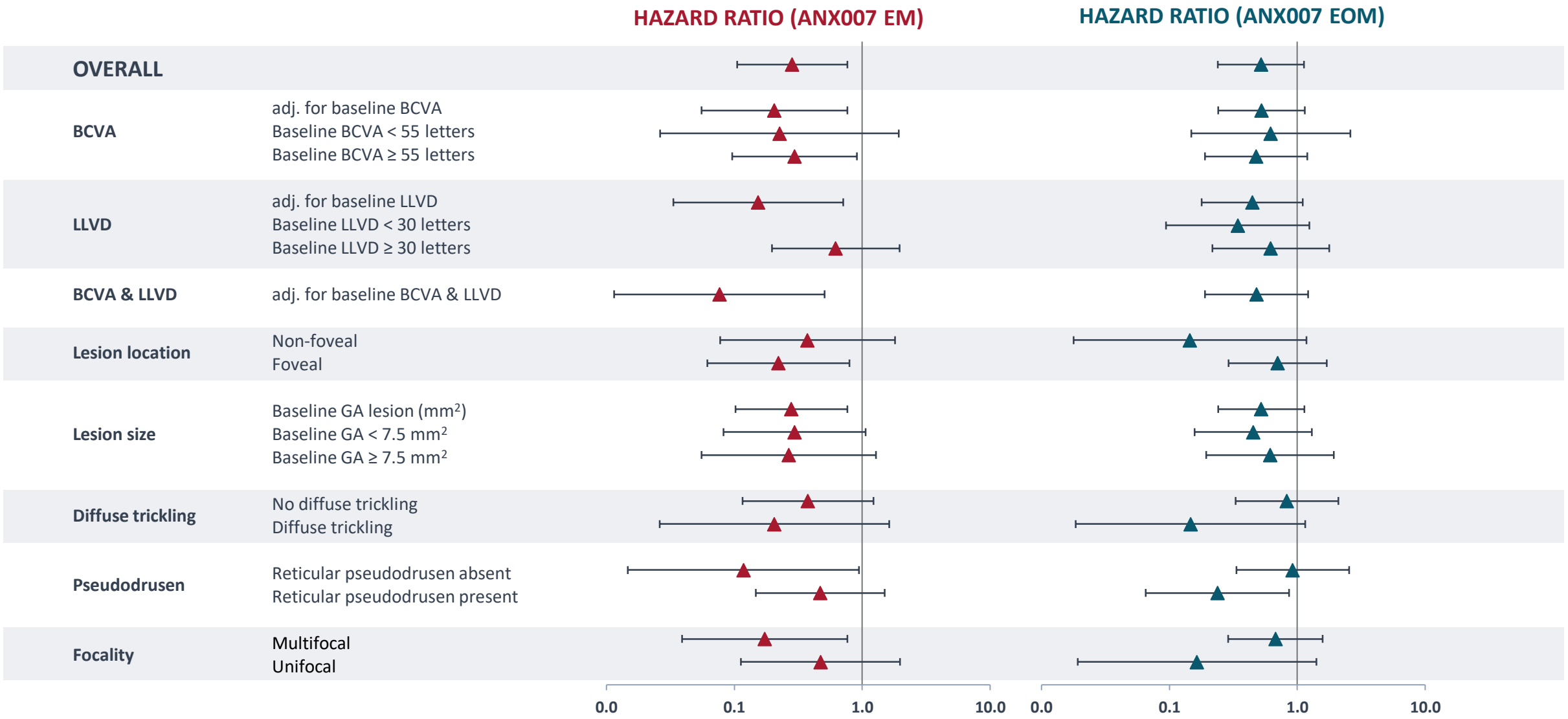
PATIENTS WITH PERSISTENT BCVA ≥15-LETTER LOSS THROUGH MONTH 12[+]



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

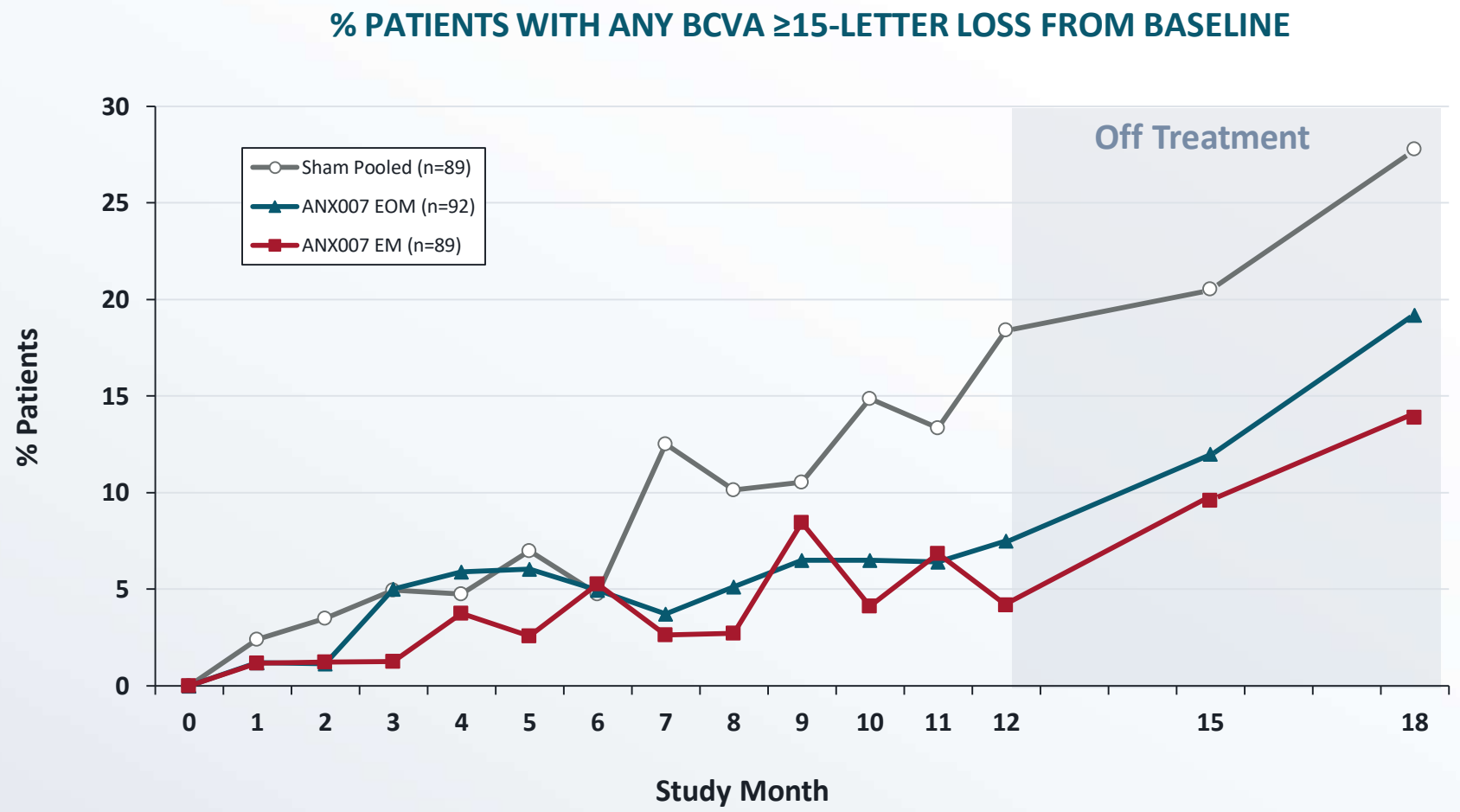
ANX007 Protection from Vision Loss Consistent Across Baseline Characteristics



*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.

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

- ✓ C1q inhibition: distinct neuroprotective MOA
- ✓ ANX007 treatment demonstrated:
  - ✓ Consistent visual function benefits
  - ✓ Highly statistically significant effect on visual acuity endpoints
  - ✓ Dose- and time-dependent effect
  - ✓ Growing effect on both vision protection and lesion growth over time
- ✓ Vision loss accelerates after treatment cessation
- ✓ ANX007 generally well-tolerated
- ✓ Phase 3 clinical and regulatory preparations are underway, including PRIME program guidance and other FDA/EMA interactions