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C1Q INHIBITION: TRANSLATING NEUROPROTECTION TO CLINICAL BENEFITS IN RETINA AND BEYOND

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Eyecelerator 2024

Chicago, IL

Forward Looking Statements

This presentation contains “forward-looking” statements about Annexon, Inc. and our industry that involve substantial risks and uncertainties. statements other than statements of historical facts, including statements regarding our clinical and preclinical programs, timing and commencement of future nonclinical studies and clinical trials and research and development programs, timing of clinical results, anticipated timing of submission of a Biologics Licensing Application, strategic plans for our business and product candidates, including additional indications which we may pursue, our financial position, runway and anticipated milestones, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “aim,” “anticipate,” “assume,” “believe,” “contemplate,” “continue,” “could,” “design,” “due,” “estimate,” “expect,” “focus,” “goal,” “intend,” “may,” “objective,” “plan,” “positioned,” “potential,” “predict,” “seek,” “should,” “target,” “will,” “would” and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

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ARCHER Phase 2 Demonstrated Significant Functional and Structural Protection in GA; Global Phase 3 Program Ongoing

- ✓ **Anti-C1q: neuroprotective MOA** protecting photoreceptor cells associated with visual acuity
- ✓ **ANX007 1st and only GA program to receive EMA PRIME Designation**
- ✓ **ANX007 ARCHER Ph 2 trial only clinical demonstration of significant-vision preservation**
  - Several lines of evidence, including: (i) 12 months on-treatment, (ii) fellow-eye, (iii) off-treatment analyses
  - Vision preservation even more robust in 'healthier eyes'
- ✓ ANX007 also demonstrated **significant protection of photoreceptors and central retinal structures important to vision**
- ✓ **ANX007 Generally well tolerated**; CNV rates consistent with sham; no reported cases of vasculitis
- ✓ **Global Phase 3** program ongoing to confirm ARCHER findings

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]

Retinal disease

- Dry AMD / GA
- Glaucoma
- Retinal ischemia

Chronic neurodegenerative disease

- Alzheimer's disease
- ALS
- Frontotemporal dementia
- Huntington's disease
- Schizophrenia
- Spinal muscular atrophy

Acute indications

- Guillain-Barré Syndrome
- 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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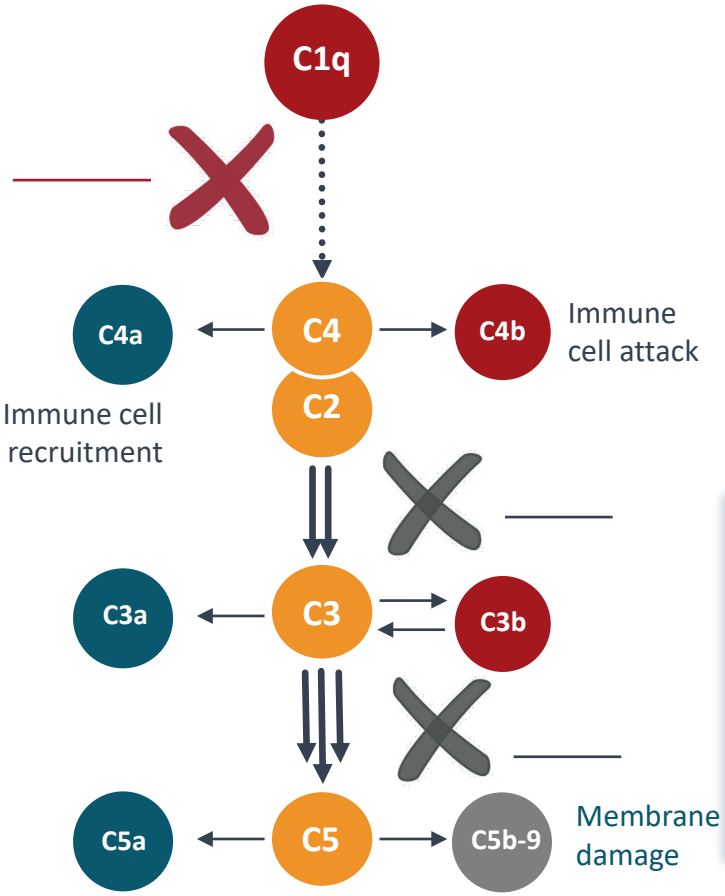
C1q Inhibition Rapidly Blocks Activation of the *ENTIRE* Classical Complement Cascade to Prevent Photoreceptor Destruction

Classical complement activates and drives harmful inflammation and tissue destruction

STOPPING AT THE START

- **Blocks upstream and downstream[1] inflammation & tissue damage**
- Before downstream bypass mechanisms (breakthrough) and pathway amplification
- **Differentiated functional outcomes shown in GBS, GA, HD and ALS**



DOWNSTREAM APPROACHES (C3/C5)

- Do not block ongoing upstream inflammatory pressure
- More susceptible to complement bypass mechanisms
- Have not resulted in significant functional outcomes in GA

[1]Lansita, et al., 2017; DOI: 10.1177/1091581817740873

GBS: Guillain-Barré Syndrome; GA: geographic atrophy; HD: Huntington's Disease; ALS: amyotrophic lateral sclerosis

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

Non-pegylated, IVT administered Fab with rapid and robust target engagement

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

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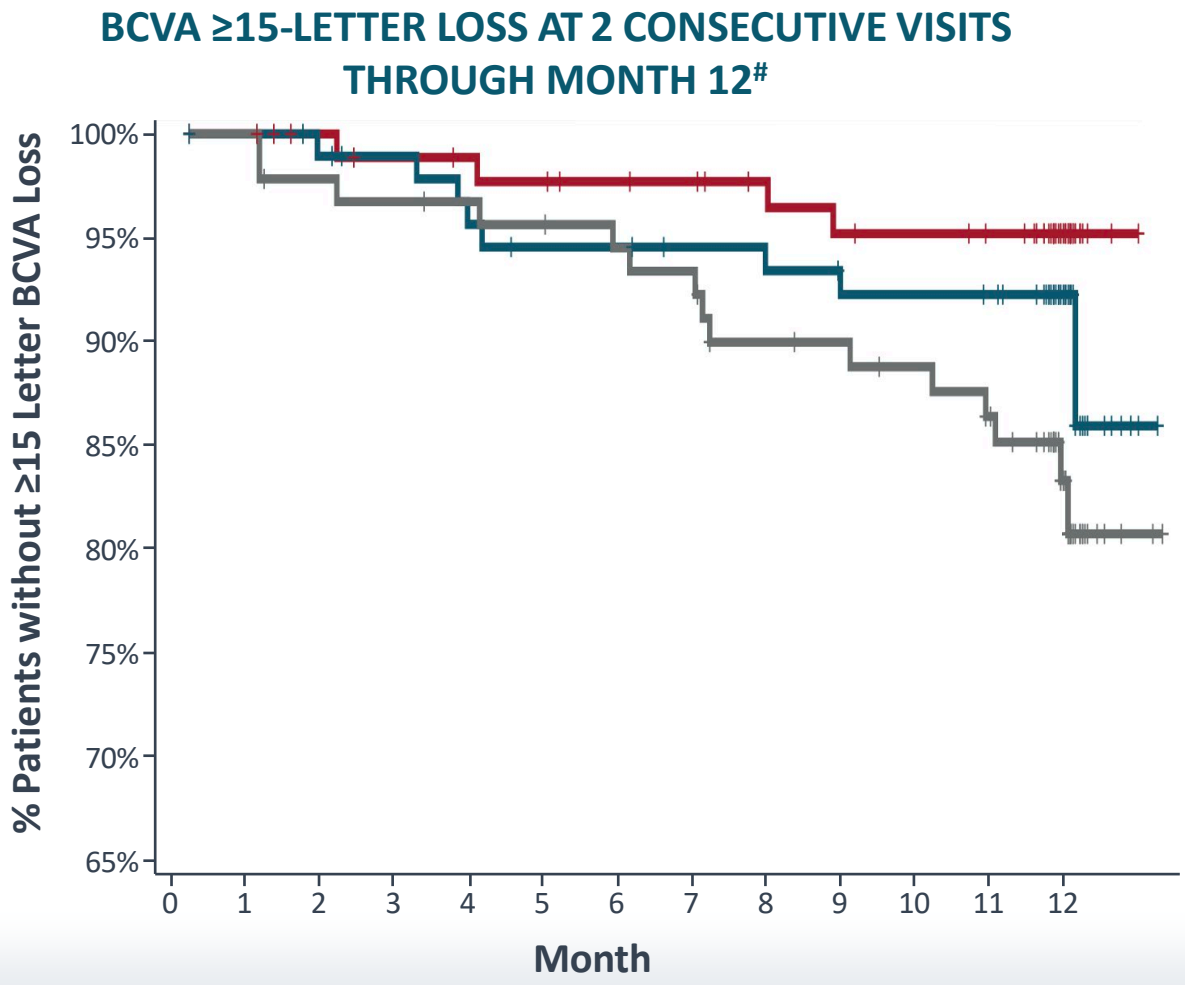
Significant Time and Dose-Dependent Protection From ≥15-Letter Vision Loss with ANX007 Monthly Treatment



EM (n=89)

73% Risk Reduction ANX007 EM

HR (CI) = 0.272 (0.090 to 0.819); p = 0.0098

EOM (n=92)

50% Risk Reduction ANX007 EOM

HR (CI) = 0.504 (0.214 to 1.190); p = 0.0788

Sham (n=89)

INCREASING ANX007 IMPACT OVER TIME

HR, hazard ratio; Nominal log-rank test (versus sham) p-values are presented;
#Persistent BCVA 15-LL at two consecutive visits including month 12 supported by ensuing (off-treatment) visit
Final data

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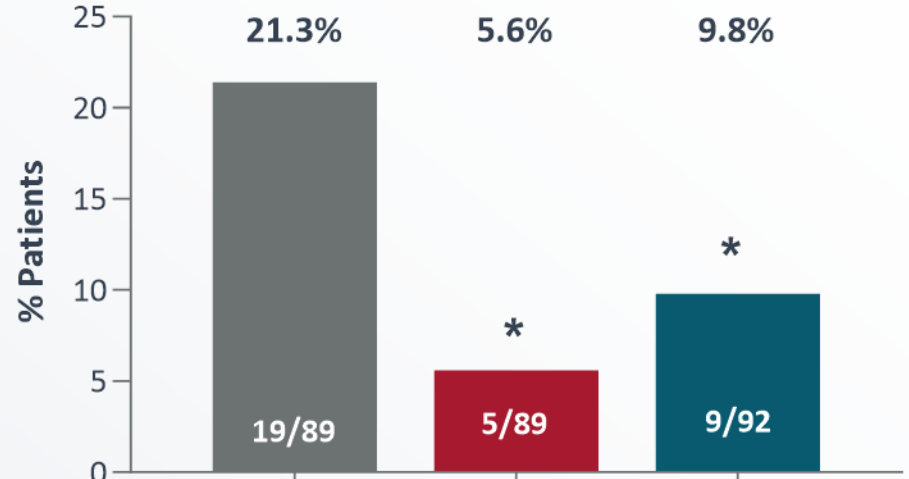
ANX007 Treatment Demonstrated Significant Protection from Vision Loss in Normal & Low Light Conditions – BCVA and LLVA

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

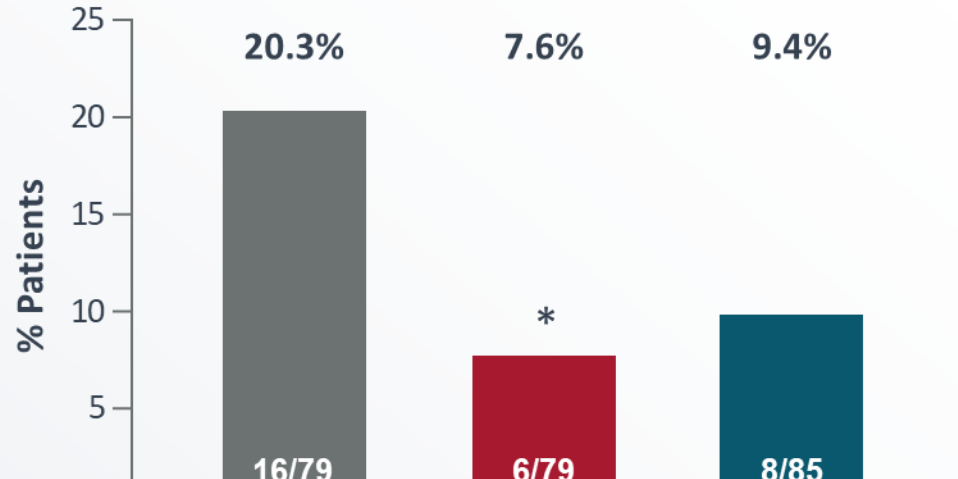
PATIENTS WITH PERSISTENT BCVA ≥15-LETTER LOSS THROUGH MONTH 12#



Nominal p-value vs sham^	---	0.0021	0.032

#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

LLVA ≥15-LETTER LOSS THROUGH MONTH 12#

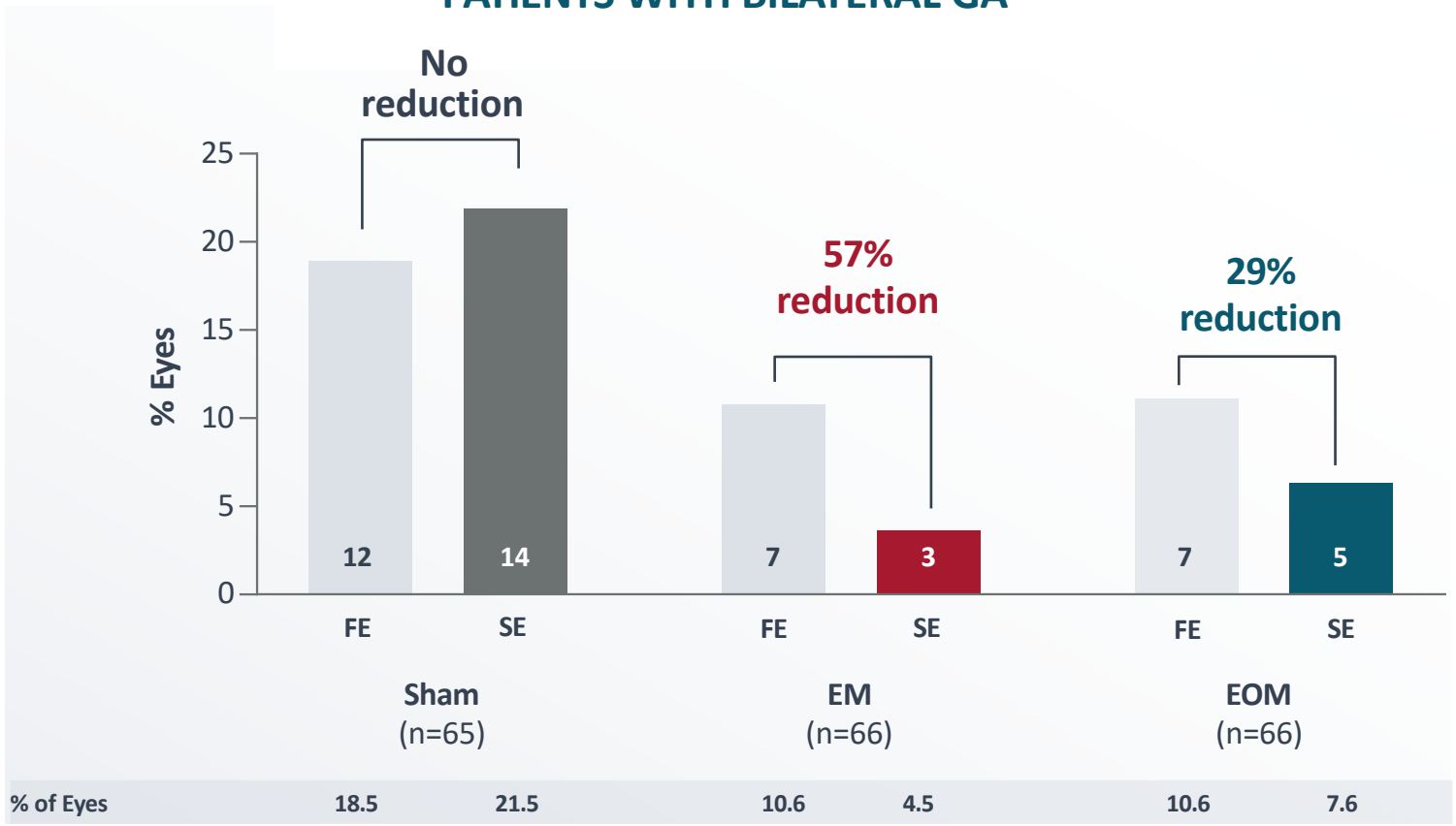


Nominal p-value vs Sham^	--	0.022	0.050

#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 Protection From Vision Loss Supported by Fellow Eye Analysis

EYES WITH ≥15-LETTER BCVA LOSS AT MONTH 12 IN ALL PATIENTS WITH BILATERAL GA



EM, every month; EOM, every other month; Pooled: EM+EOM; FE, fellow eye; SE, study eye
All patients with bilateral GA were included due to small sample size

- **Sham: No reduction in BCVA vision loss in study vs. fellow eye**
- **ANX007: Dose dependent protection from vision loss in ANX007 treated study eyes relative to fellow eyes**
  - EM: 57% reduction in 15-letter loss
  - EOM: 29% reduction in 15-letter loss

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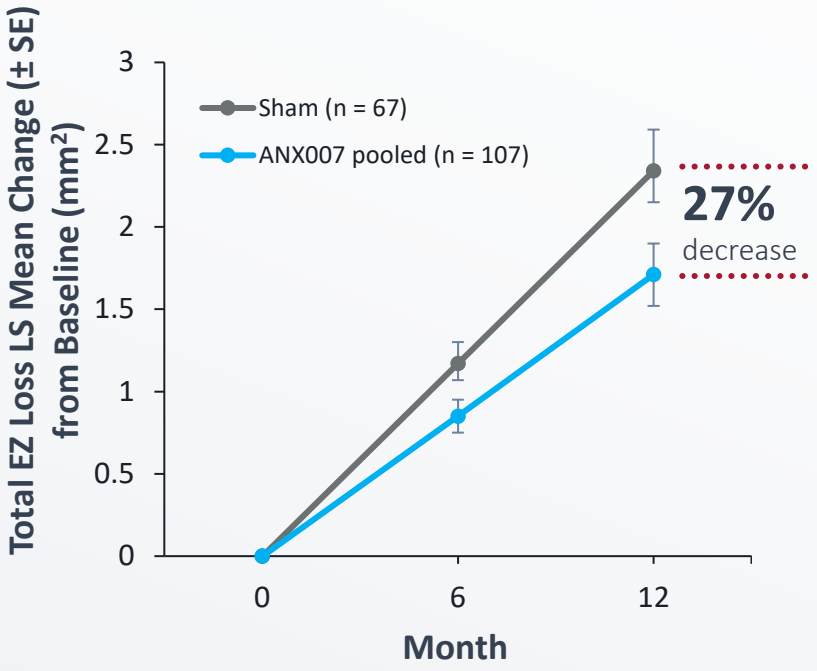
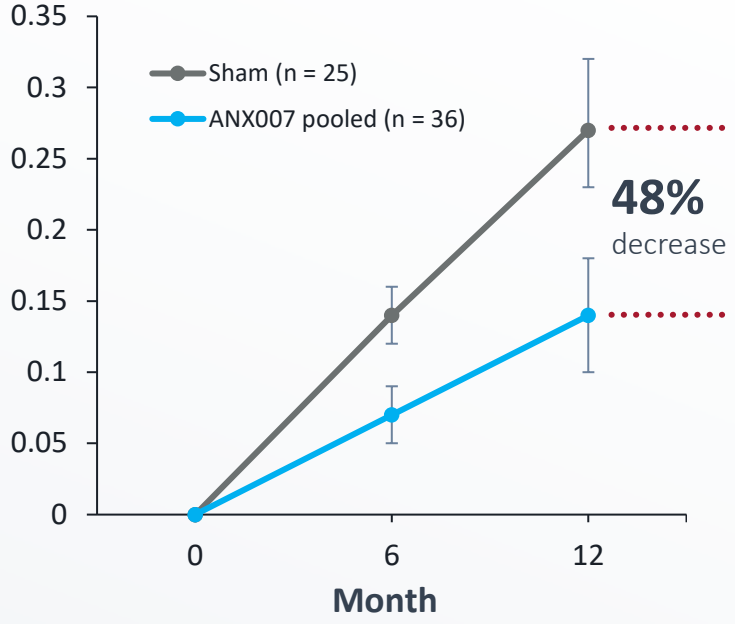
EZ Analysis: Significant Photoreceptor Protection with ANX007

More robust protection with ANX007 in central subdomains - area best correlated with vision

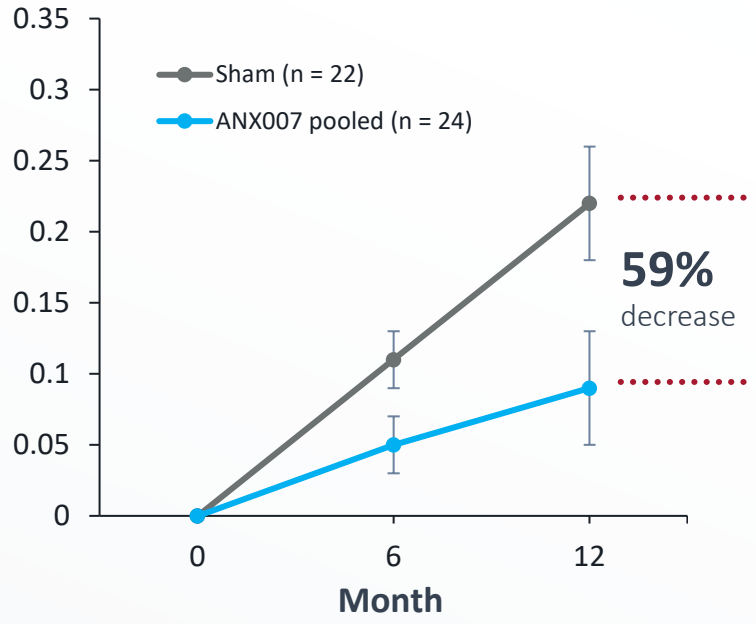
PAN-MACULA



CENTRAL 2.0 MM



CENTRAL 1.5 MM



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

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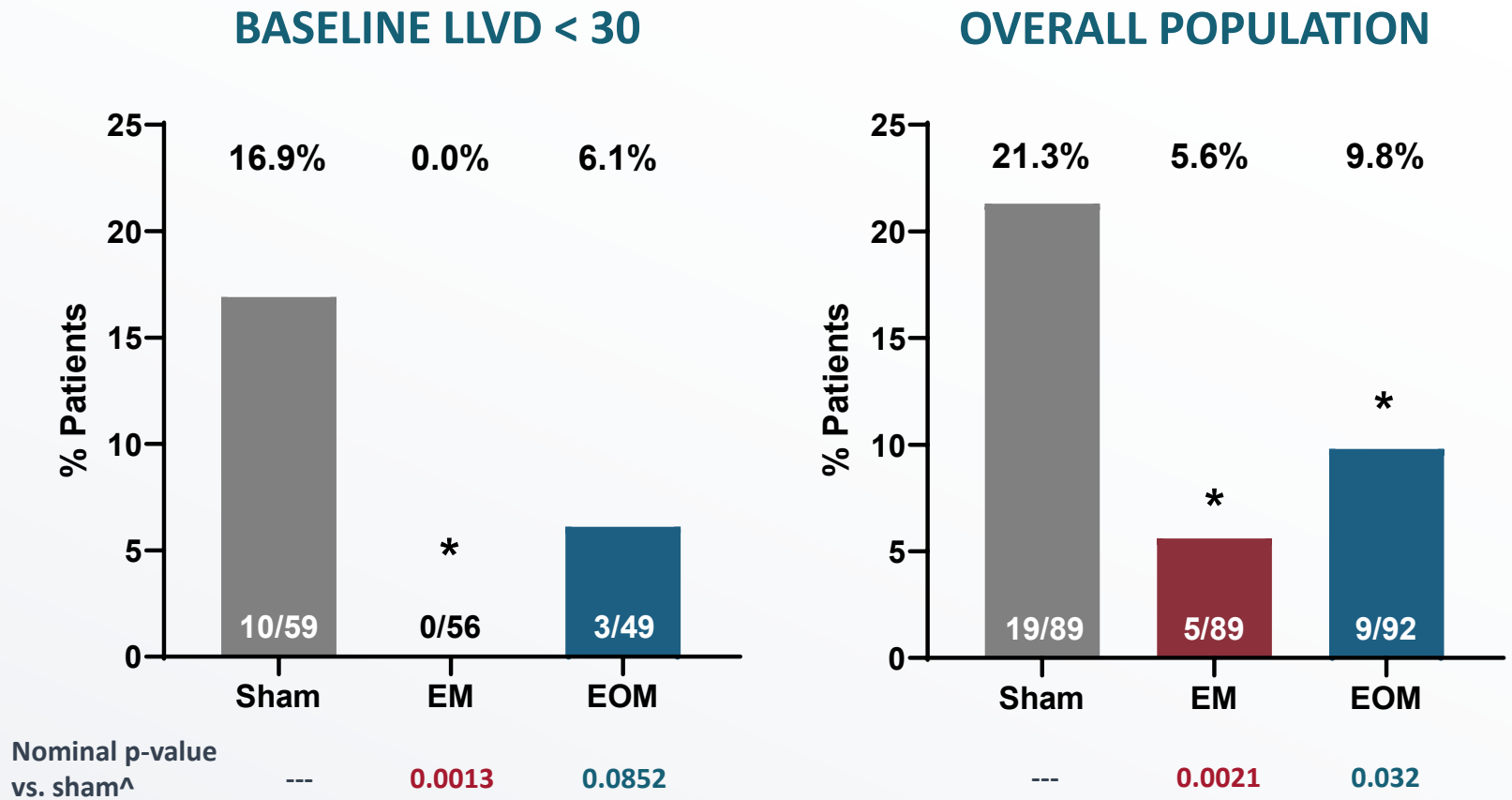
ANX007 Strongest Vision Preservation (BCVA 15-Letter Loss) Demonstrated in Eyes with Less Advanced Dry AMD / GA

Less low luminance vision deficit = more robust ANX007 response

BCVA PERSISTENT 15-LETTER THROUGH MONTH 12#



Nominal p-value vs. sham^	---	0.0013	0.0852

	---	0.0021	0.032

#Persistent for two consecutive visits thought month 12 or at last study visit
^Nominal p-value from a Cochran Mantel-Haenszel test (General Association)

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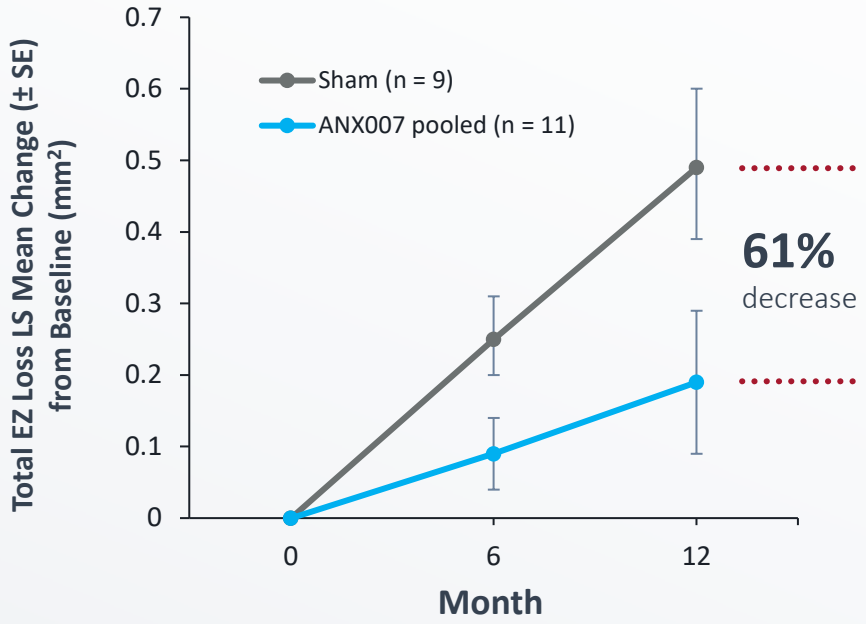
ANX007 Structural Benefits Also Stronger in Eyes with Less Advanced Dry AMD / GA

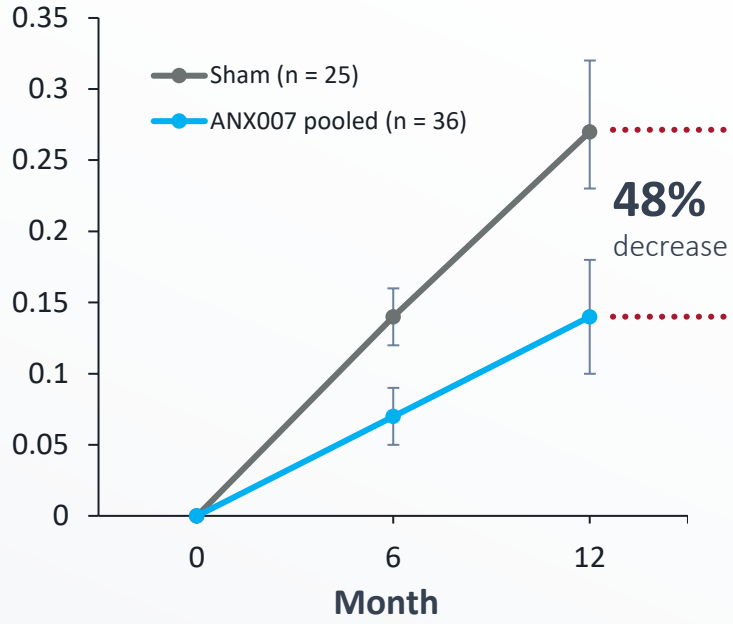
More EZ remaining = more pronounced ANX007 response

TOTAL EZ LOSS (EZ= 0µm)
CENTRAL 2.0 mm SUBDOMAIN

< 80% EZ LOSS @ BASELINE



< 98% EZ LOSS @ BASELINE



Nominal p-value vs sham^		
	ANX007 Pooled vs Sham 0.0575	ANX007 Pooled vs Sham 0.0218

^Nominal p-values from a linear mixed model for repeated measures model (slope) analysis; Heidelberg Spectralis OCT population with baseline OCT data

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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			

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

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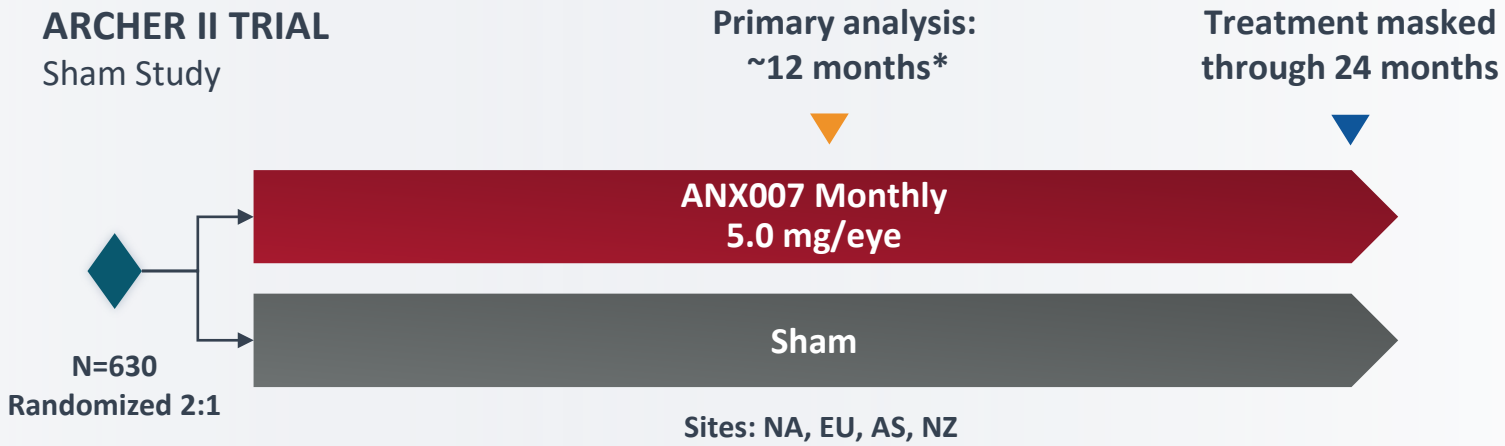
ARCHER II: ANX007 Global Phase 3 Program ENROLLING Now

PRIME designation from EMA



PRIMARY ENDPOINT

Persistent BCVA ≥15-Letter Loss through ~12 months*

*Primary analysis based on accumulation of BCVA ≥15-letter loss target events assessed between months 12-18 from initiation of dosing

SECONDARY ENDPOINTS

Safety, Low Luminance VA (LLVA), Ellipsoid zone (EZ)

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ANX007: A Novel Neuroprotective Approach Demonstrating Consistent and Clinically Meaningful Protection in GA - ARCHER II Phase 3 Program Now Enrolling

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

ANX007 protected retinal structures closely associated with visual function – photoreceptors and foveal RPE

ANX007 most profound effects in eyes with **less-advanced disease**

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

Global Phase 3 program NOW ONGOING