#### ANNEXON

biosciences



ARCHER Trial in Geographic Atrophy: Protection from Functional and Structural Loss



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This presentation contains "forward-looking" statements about Annexon, Inc. and our industry that involve substantial risks and uncertainties. All statements of historical facts, including statements regarding topline data from the ARCHER Phase 2 trial and post-hoc analyses, our clinical and preclinical programs, timing and commencement of future nonclinical studies and clinical trials and research and development programs, timing of clinical results, 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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These and other risks are described in greater detail under the section titled "Risk Factors" contained in our Annual Report on Form 10-K and Quarterly Reports on Form 10-Q and our other filings with the Securities Exchange Commission (SEC) Annual Report on Form 10-K filed with the Securities Exchange Commission (SEC) on March 26, 2024 and our other filings with the SEC from time to time. All forward-looking statements in this presentation speak only as of the date of this presentation. Except as required by law, we undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise.

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A bold mission to free the body, brain and eye from complement-mediated disease



#### **Overview of ANX007 Geographic Atrophy Program**

Pioneering upstream classical complement trial with demonstrated functional benefit

- ✓ Unique MOA targeting classical complement inflammation where it starts
- ✓ Preclinical classical complement inhibition protected photoreceptor cell loss and function
- ✓ ARCHER 1st clinical demonstration of significant, dose & time-dependent vision preservation
  - Vision preservation supported by multiple lines of evidence, including: 12 months on-treatment, fellow-eye, foveal status and off-treatment analyses
  - Clinical impact consistently improved over time on BCVA ≥15-letter loss measures
- ✓ Significant protection of photoreceptors, as measured by EZ analysis
- ✓ Generally well tolerated; no CNV increase in treated vs. sham; no reported cases of vasculitis
- ✓ ANX007 1st and only EMA PRIME Designation in GA based on preclinical & ARCHER data set
- ✓ Robust global Phase 3 program to confirm ARCHER findings starting mid-2024



# ANNEXON biosciences **Anti-C1q Mechanism of Action**

## Classical Complement-Mediated Neurodegeneration Extensively Researched in Ophthalmic and Neurological Diseases

Functional clinical benefit previously demonstrated in Huntington's disease and ALS, and now in GA



Ben Barres, M.D., Ph.D. Discoverer of C1q Technology Scientific Co-Founder, Annexon

#### Anti-C1q protective in several models, including:

- Geographic atrophy (photoreceptor damage)
- Glaucoma
- Retinal ischemia
- · Huntington's disease
- Amyotrophic lateral sclerosis
- Alzheimer's disease
- Frontotemporal dementia
- Spinal muscular atrophy
- Traumatic brain injury

#### ANTI-C1q PROTECTS AGAINST SYNAPSE LOSS AND NEURODEGENERATION

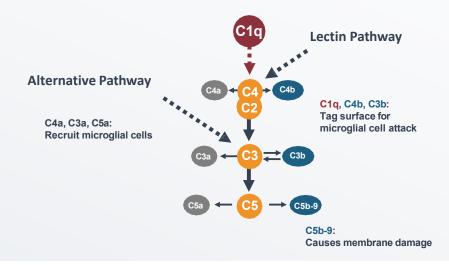
- Discovered by Annexon co-founder, Ben Barres, spawning an entire field and validated in multiple labs<sup>1</sup>
- Synapse loss correlates with functional decline<sup>2</sup>
- Synapse loss precedes neuronal loss<sup>3</sup>

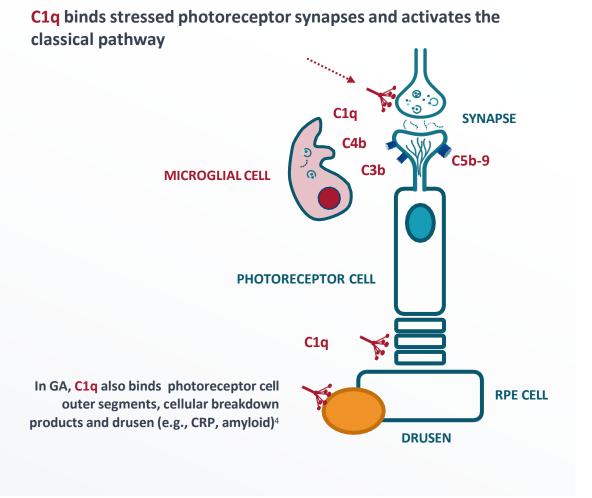


#### **Anti-C1q: A Distinct Neuroprotective Mechanism**

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

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







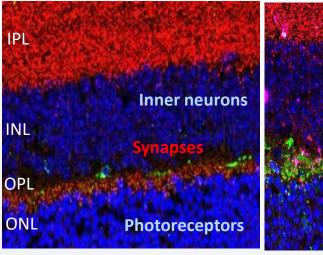
## Synapses/C1q/Microglia

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

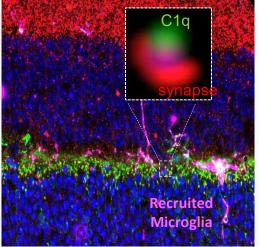


#### C1q Deposition on Photoreceptor Cells and Synapses with Light-Induced Damage

#### **CONTROL**



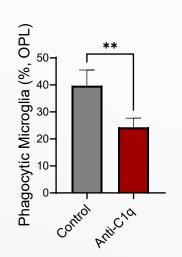
3 DAYS POST WHITE LIGHT DAMAGE



Tassoni, et al., Annexon on file

#### **Anti-C1q Protected Photoreceptors and Function**



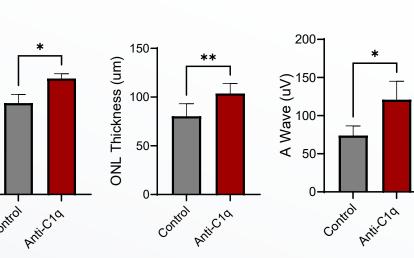


PROTECTED
PHOTORECEPTOR
SYNAPSES

Synaptic Density in OPL



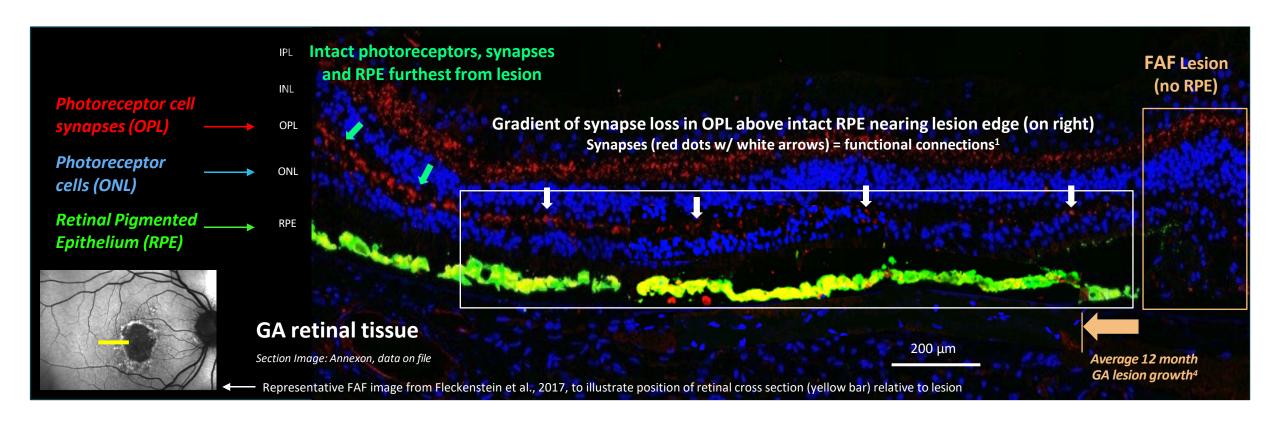






#### Photoreceptor Cells, Synapses & Function Lost Prior to RPE in GA

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



## ANNEXON biosciences

**ARCHER Trial Overview** 



## Geographic Atrophy (GA): Progressive and Life-altering Disease that Remains a Leading Cause of Blindness in Elderly People

- Advanced form of age-related macular degeneration (AMD)
- Chronic, progressive neurodegenerative disease of the eye with irreversible vision loss
- 1M people diagnosed in US; 2.5M in EU
- Diagnosis can be traumatic and impact the social and financial aspects of patients lives, including reading, daily activities and recognizing faces
- No currently approved therapies have demonstrated preservation of visual function
- Urgent unmet need to protect against vision loss



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

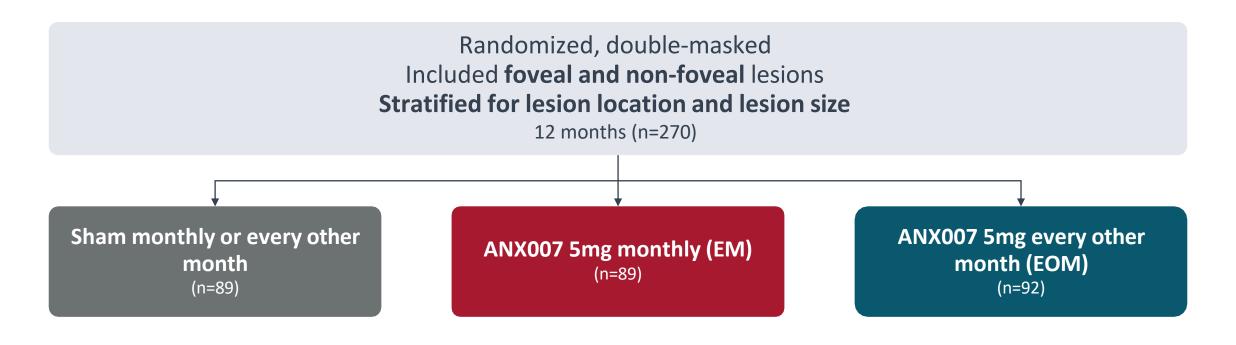
#### **ANX007**

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</p>
- ✓ Dosing: 5 mg / 100 microliters; 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 functions¹

#### **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%
Foveal Lesion  GA Lesion Size (mm²), mean (SD)	49.4% 7.28 (3.99)	57.3% 7.28 (3.96)	53.3% 7.53 (4.10)
GA Lesion Size (mm²), mean (SD)	7.28 (3.99)	7.28 (3.96)	7.53 (4.10)

#### **Discontinuations Consistent with Previous GA Studies**

	SHAM POOLED (N=89)	ANX007 EM (N=89)	ANX007 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	

#### **BCVA: Widely Accepted Functional Endpoint of Visual Acuity**

BCVA 15-letter change or Mean BCVA change used in multiple sham-controlled pivotal trials

#### **BEST CORRECTED VISUAL ACUITY (BCVA)**

15-Letter Loss

20/60 to 20/120 vision



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



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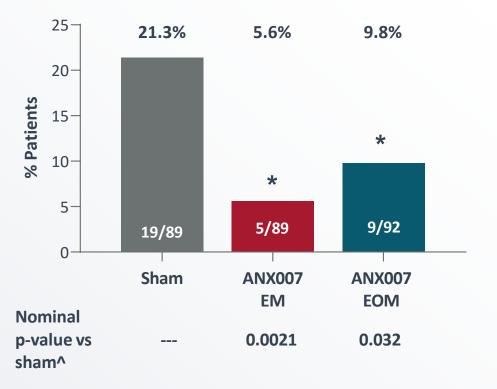
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ARCHER Trial
Visual Acuity Results



## **ANX007** Demonstrated Statistically Significant Protection From Vision Loss as Measured by BCVA ≥15-Letter Loss (All Patients)

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

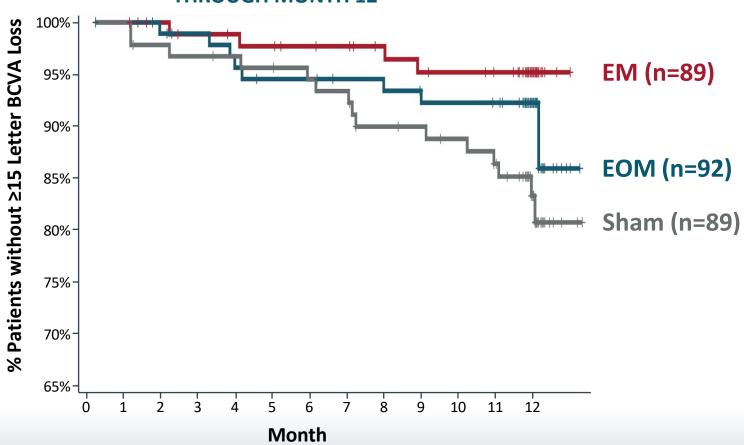


 $^{\#}$ Persistent for two consecutive visits through month 12 or at last study visit  $^{n}$ Nominal p-value from a Chi-square test in ITT population:  $^{*}$  Nominal p < 0.05 Final data

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

## Significant, Time-Dependent Protection From ≥15 Letter Vision Loss with ANX007 Monthly Treatment (All Patients)

#### BCVA ≥15-LETTER LOSS AT 2 CONSECUTIVE VISITS THROUGH MONTH 12#



#### 73% Risk Reduction ANX007 EM

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

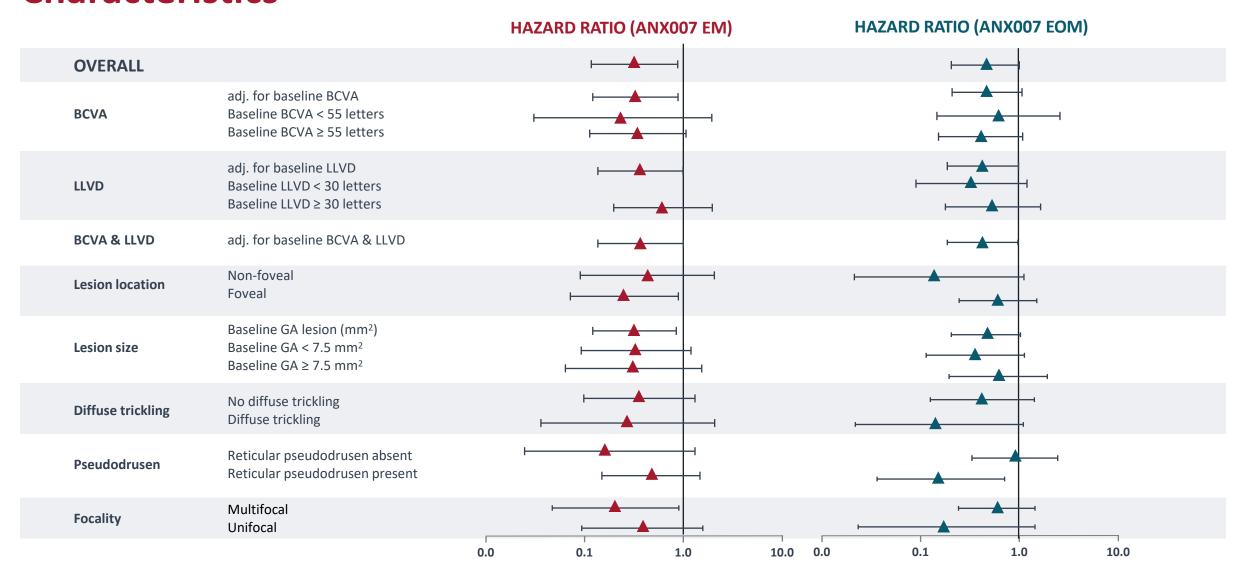
#### 53% Risk Reduction ANX007 EOM

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

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

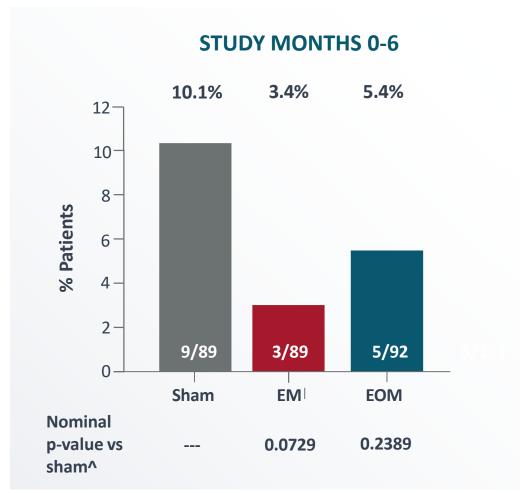
## **ANX007 Protection from Vision Loss Consistent Across Baseline Characteristics**

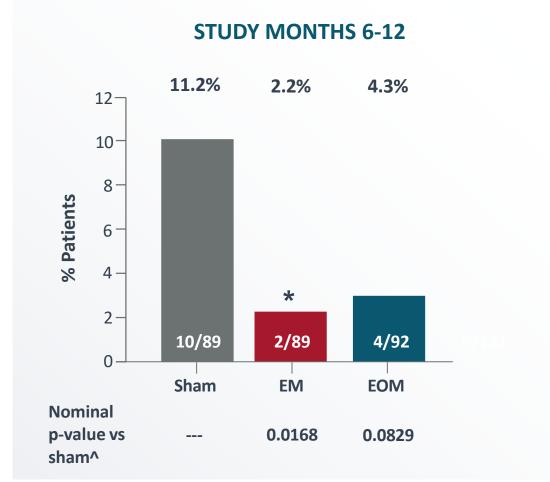




## **ANX007 Effect on BCVA ≥15-Letter Loss Improves with Longer Treatment**

#### PATIENTS WITH PERSISTENT BCVA ≥15-LETTER LOSS





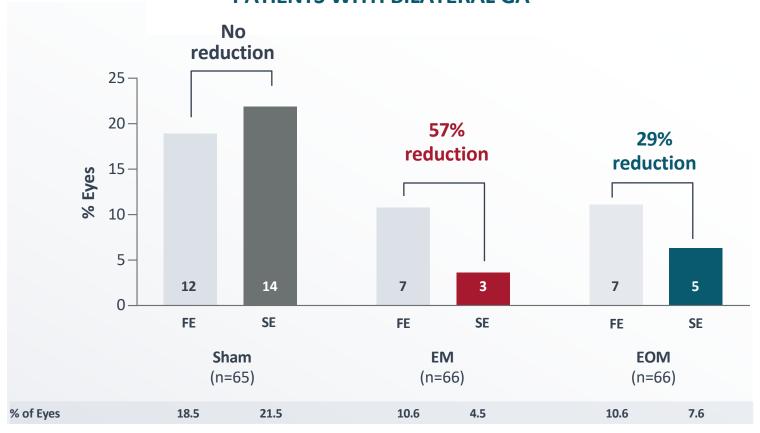
\*Persistent for two consecutive visits through month 12 or at last visit; ^Nominal p-value from a Chi-square test in ITT population; \* Nominal P < 0.05

**Increasing ANX007 Impact Over Time** 



#### **Protection From Vision Loss Supported by Fellow Eye Analysis**

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

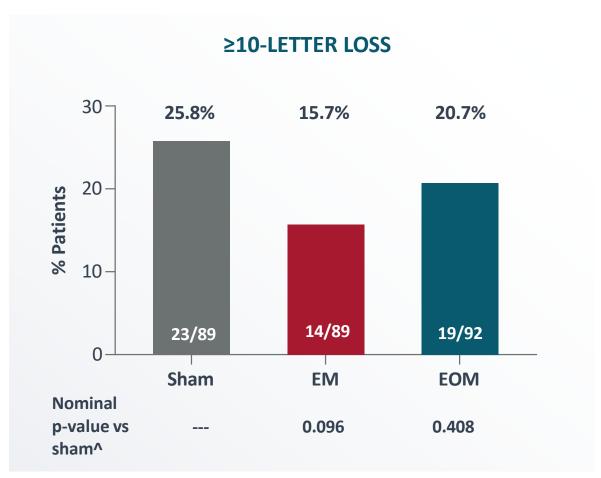


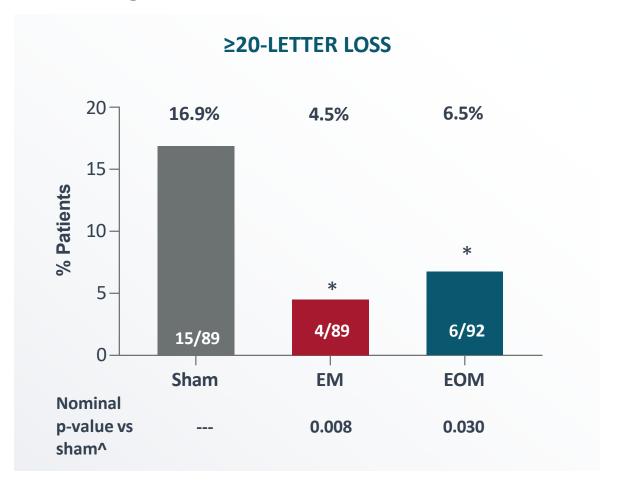
- Sham: No reduction in BCVA vision loss study vs. fellow eye
- Dose dependent protection from vision loss in ANX007 treated study eyes relative to fellow eyes
  - EM: 57% reduction in 15-letter loss
  - EOM: 29% reduction in 15-letter loss

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

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

#### Persistent BCVA Vision Loss Through Month 12<sup>+</sup>





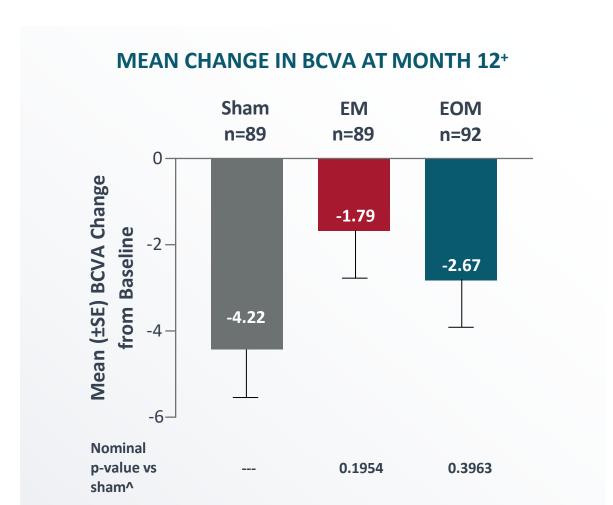


 $<sup>\</sup>ensuremath{^{\scriptscriptstyle +}}\text{Persistent}$  for two consecutive visits through month 12 or at last visit

<sup>^</sup>Nominal p-value from a Chi-square test in ITT population

<sup>\*</sup> 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<sup>1,2,3</sup>

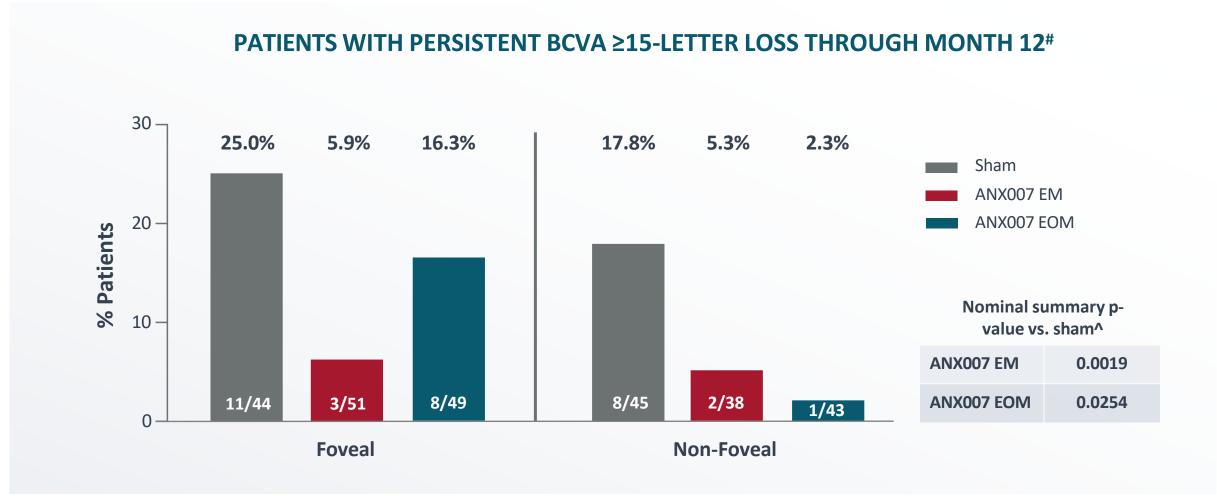
<sup>&</sup>lt;sup>1</sup>Liao et al (2020) *Ophthalmology* 127: 186-195; <sup>2</sup>Holtz et al (2018) *JAMA Ophthalmology* 136:666-677; <sup>3</sup>Heier et al, *Retina Society* 2022



<sup>\*</sup>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.

<sup>^</sup>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

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

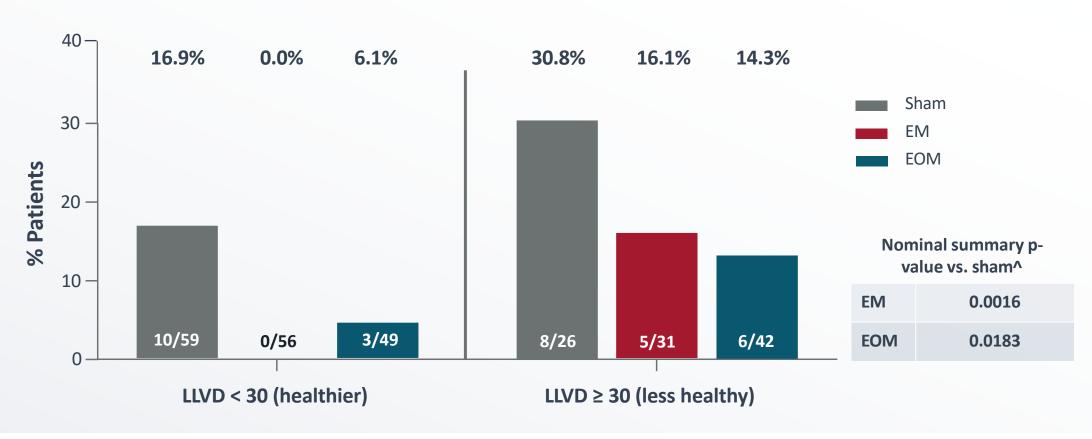


<sup>\*</sup>Persistent for two consecutive visits at any time through month 12 or at last study visit

^Nominal p-value from a Cochran Mantel-Haenszel test (General Association) in ITT population
Final data

## **ANX007** Protected Against Vision Loss BCVA ≥15-Letter Loss Regardless of Retina Health at Baseline

#### PATIENTS WITH PERSISTENT ≥15-LETTER LOSS INCLUDING MONTH 12#

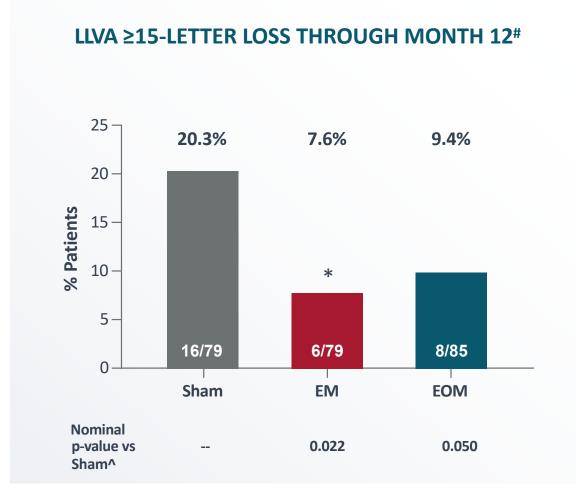


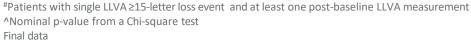
<sup>\*</sup>Persistent for two consecutive visits including month 12

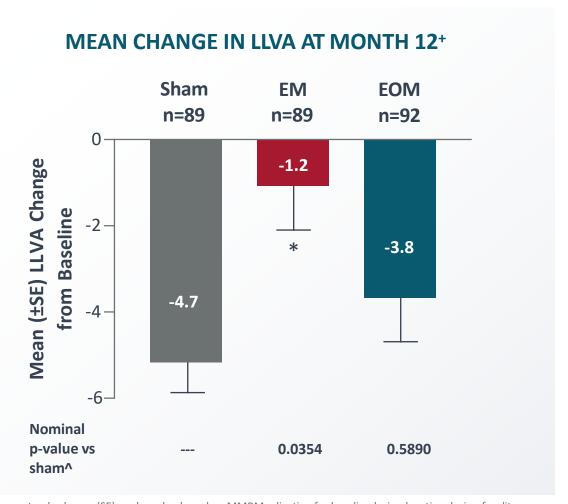


<sup>^</sup>Nominal p-value from a Cochran Mantel-Haenszel test (General Association) in ITT population

## Consistent Protection From Vision Loss with ANX007 Treatment Also Demonstrated with LLVA (All Patients)







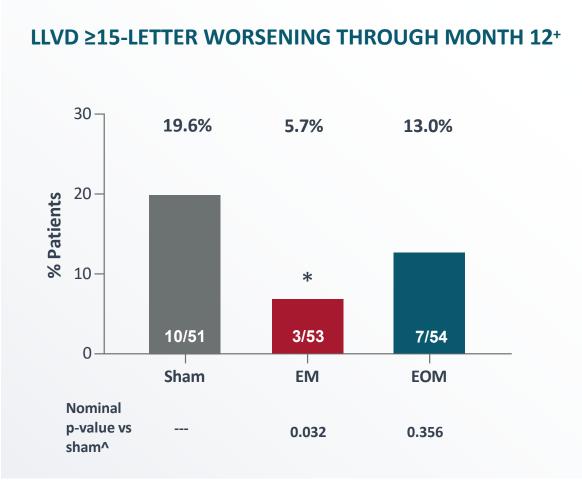
<sup>&</sup>lt;sup>†</sup>Mean, standard error (SE), and p-value based on MMRM adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.

Final data

<sup>^</sup>Nominal p-value from a Chi-square test in ITT population

<sup>\*</sup> Nominal P < 0.05

## Prespecified Secondary Analysis: ANX007 Provided Consistent Protection from Vision Loss by LLVD



<sup>+</sup>in subjects with BCVA ≥55



<sup>^</sup>Nominal p-value from a Chi Square test

<sup>\*</sup>p<0.05

#### **BCVA ≥15-Letter Loss Accelerated After Cessation of Treatment**

Visual Function Loss Paralleled Sham in Off-Treatment Period (All Patients)

#### PATIENTS WITH ANY BCVA ≥15-LETTER LOSS FROM BASELINE



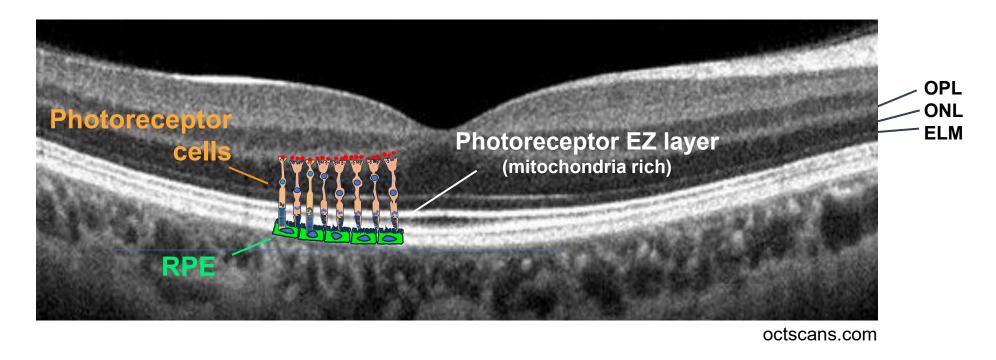
- Low frequency (<10% per timepoint) of single BCVA ≥15-letter losses in EM- and EOM-treated groups during 12-month treatment period</li>
- BCVA ≥15-letter loss frequency increased (10% or greater) in offtreatment period for EM and EOM groups, paralleling sham behavior

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ANX007 Impact on Retinal Structure



## **Change in OCT Ellipsoid Zone (EZ) Directly Measures Photoreceptor Anatomy**

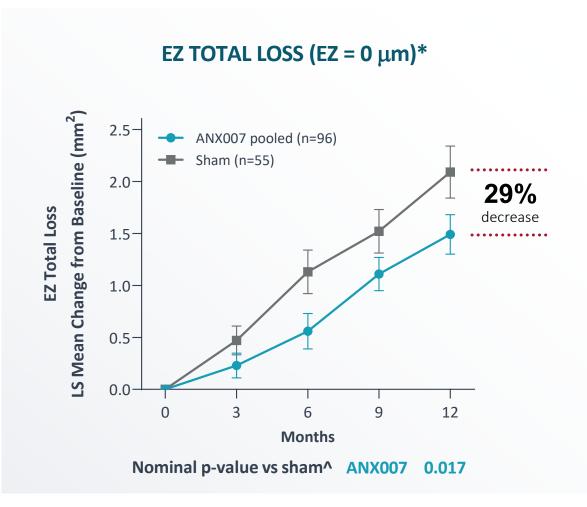


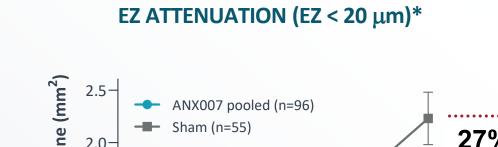
#### **ARCHER EZ Population**

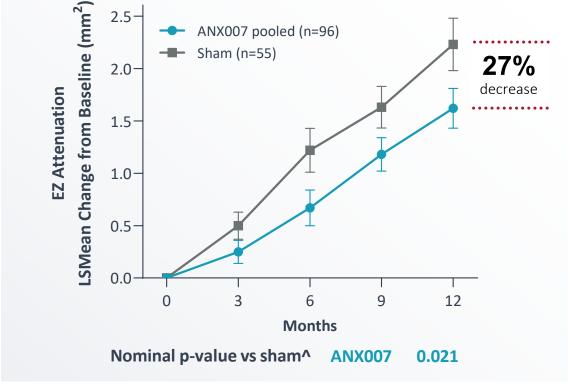
Sham	ANX007 EM	ANX007 EOM	Total
71	60	62	193

- 193 patients with OCT scans from Heidelberg Spectralis
- Patient demographics and study eye characteristics were generally well balanced across groups
- Same treatment effect between sham, EM and EOM groups as in whole study population

## **ANX007** Significantly Protected Photoreceptors Through 12 Months (Foveal and Non-Foveal Patients)



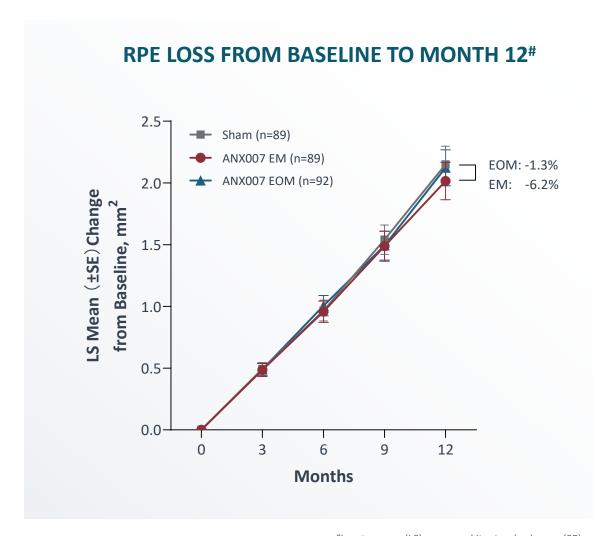


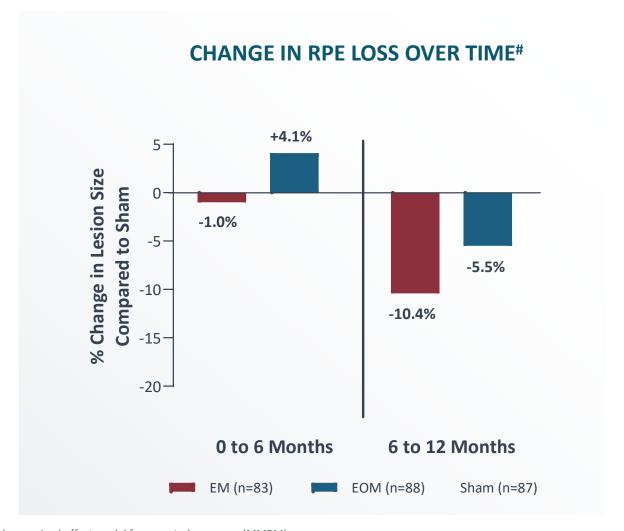


<sup>^</sup>Nominal p-values from a mixed model for repeated measures (MMRM) analysis; Heidelberg Spectralis OCT population with baseline OCT data (n=151)

<sup>\*</sup>Two treatment groups (EM and EOM) were not different statistically

## ANX007 Did Not Significantly Reduce Overall RPE Loss, but Effects Increased Over Time (FAF Assessment in All Patients)

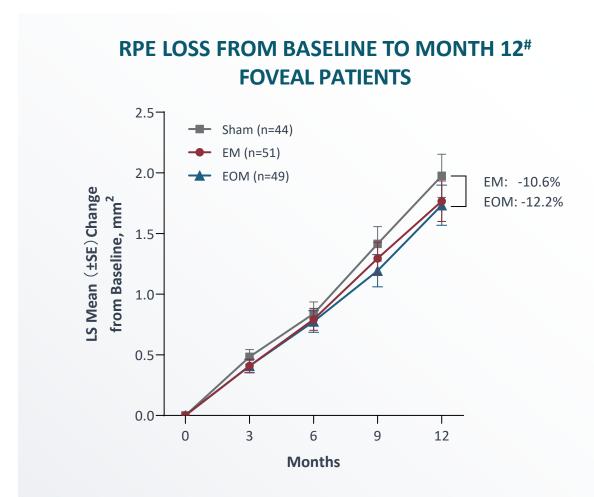


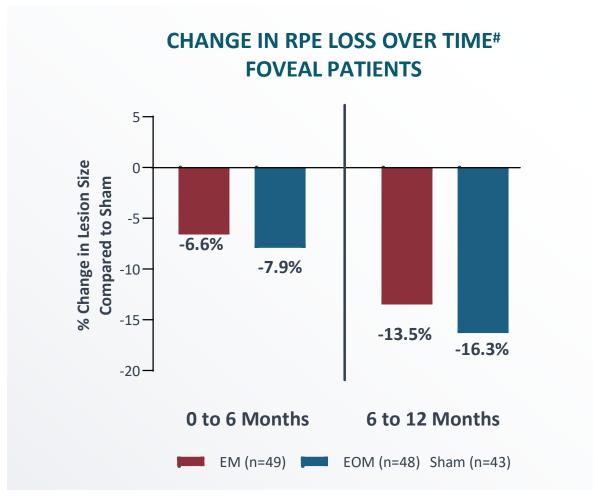


\*Least-square (LS) mean and its standard error (SE) are based on a mixed-effect model for repeated measures (MMRM) adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.

## ANX007 Demonstrated Stronger Impact on RPE Loss in Patients with Foveal Involvement at Baseline (FAF Assessment)

Greater protection of RPE in region responsible for visual acuity

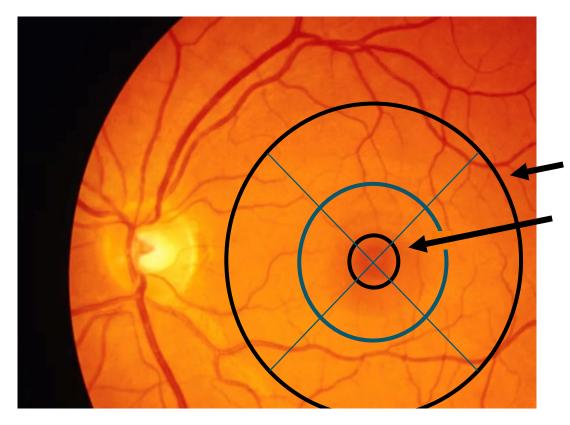




"Least-square (LS) mean and its standard error (SE) are based on a mixed-effect model for repeated measures (MMRM) adjusting for baseline lesion location, lesion focality, baseline GA lesion, and the baseline GA lesion by visit interaction.

#### RPE Loss within the Central Fovea Correlates with BCVA Loss<sup>1</sup>

#### Correlation in central 1mm seen as early as 6 months



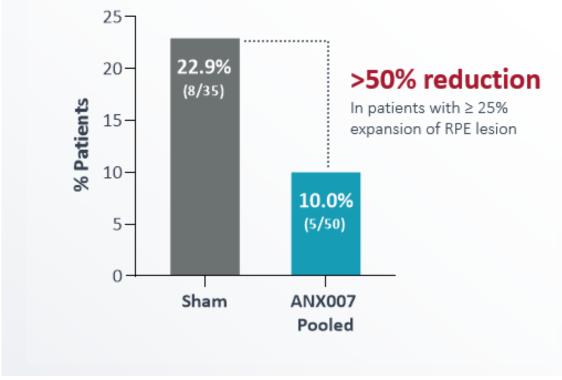
#### **Spearman Correlation Coefficients Comparing the Changes in RPE Area with BCVA Change Over Time**

Location	Month 6	Month 12	Month 18
Full 6 mm diameter	p=0.59	p=0.15	p=0.03
1mm foveal center	p=0.03	p=0.001	p<0.0001

- Correlation in central 1mm as early as 6 months
- Overall lesion growth correlates after 18 months

## ANX007 Provided >50% Reduction in the Number of Patients with Foveal RPE Loss—the Region Best Correlated with Visual Acuity Loss¹

## PATIENTS EXPERIENCING SUBSTANTIAL RPE LOSS IN CENTRAL 1MM AT 12 MONTHS#



RPE Loss in Central 1mm Diameter Slowed with ANX007 Treatment

\*Patients with at least 25% of RPE in the central 1mm unoccupied at baseline; includes only patients with Heidelberg Spectralis OCT scans (overall n=194); substantial RPE loss defined as 25% absolute loss of RPE

#### **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 <sup>+</sup>	0	2 (2.2%)	1 (1.1%)	
Ischemic Optic Neuropathy <sup>+</sup> - No Cases Reported				

<sup>^</sup>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

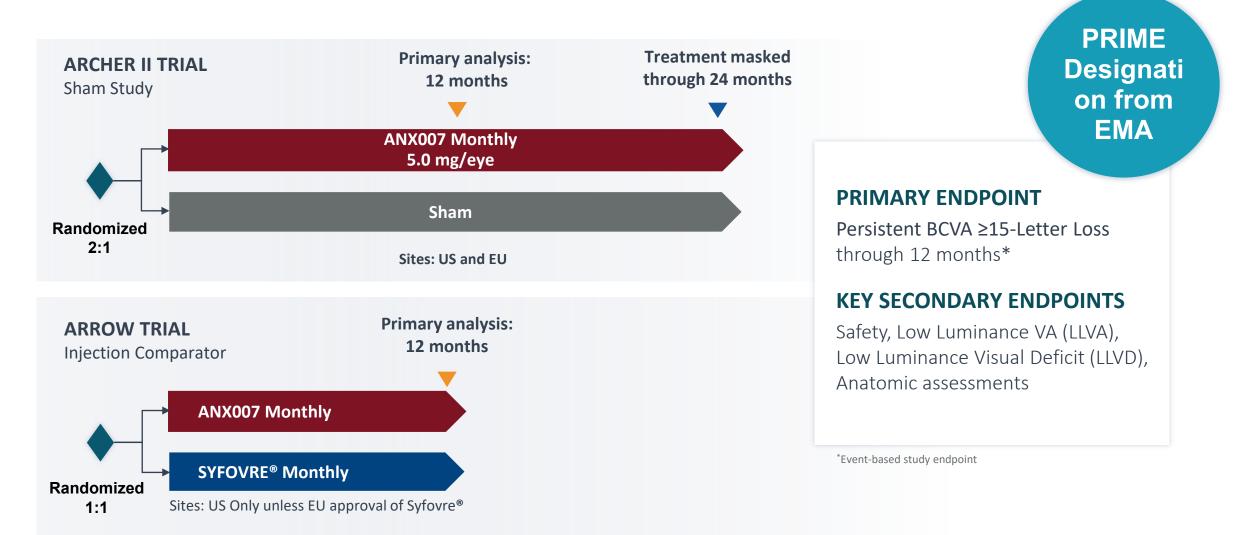
KP on endothelium, prior treatment with topical steroids No Vasculitis

<sup>\*</sup>Event Verbatim term listed

## ANNEXON biosciences Phase 3 Program Overview

#### ANX007 Global GA Pivotal Program to begin Mid-2024

ARCHER II initiation in mid-2024; ARROW trial initiation in late-2024



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

**Blocking C1q for neuroprotection**, prevented synapse loss and protected photoreceptors from elimination

**ANX007**, an anti-C1q Fab antibody administered IVT, **protected against the loss of visual acuity** in the Phase 2 ARCHER study

**ANX007** also **demonstrated protection of retinal structure**, particularly those structures closely associated with visual function – **photoreceptors and foveal RPE** 

ANX007 treatment was **generally well-tolerated**; no CNV increase; no reported cases of vasculitis

Phase 3 program aligned with regulators and initiating mid-2024



To the patients, families, caregivers, physicians and medical teams who participated in our trial, we are eternally grateful for your support and contributions!

To our employees, collaborators and advisors, thank you for your **Warrior Spirit and All For One** commitment!







