Is the Confirmed Loss of 15 or More ETDRS Letters a Meaningful and Consistent Indicator of Clinically Relevant Visual Function Loss in Dry AMD?

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- Affamed Therapeutics – Grant
- Alexion – Grant
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- Apellis – Grant, Consultant/Advisor
- AsclepiX – Grant
- Ashvattha Therapeutics – Consultant/Advisor
- Astellas – Grant, Consultant/Advisor
- Aviceda Therapeutics – Grant
- Boehringer Ingelheim – Consultant/Advisor
- Curacle – Grant, Consultant/Advisor
- Eyebio – Grant
- Eyepoint Pharmaceuticals – Grant, Equity/Stockholder –Public
- Genentech – Grant, Consultant/Advisor, Speaker
- Kalaris Therapeutics – Grant
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- Kriya Therapeutics – Consultant/Advisor, Equity Options – Private
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- Neurotech – Consultant/Advisor
- Ocular Therapeutix – Consultant/Advisor, Equity/Stockholder –Public
- Opthea – Grant, Consultant/Advisor
- Opus Genetics– Grant, Consultant/Advisor
- Outlook Therapeutics – Consultant/Advisor,
- Pykus Therapeutics – Grant
- Regeneron – Consultant/Advisor, Grant, Speaker
- Roche – Consultant/Advisor
- Stealth BioTherapeutics – Consultant/Advisor
- 4DMT - Grant

BCVA 15-Letter Change from Baseline Historically Used in Many Pivotal Trials

BEST CORRECTED VISUAL ACUITY (BCVA)

15-Letter Loss

Example: 20/60 to 20/120

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
Vabysmo	Mean BCVA change
Iluvien	BCVA ≥15 letter
Retinal Vascular Occlusion (BRVO/CRVO)	
Lucentis	BCVA ≥15 letter
Eylea	BCVA ≥15 letter
Ozurdex	BCVA ≥15 letter

Visual Acuity Outcomes in GA from Previously Published Datasets

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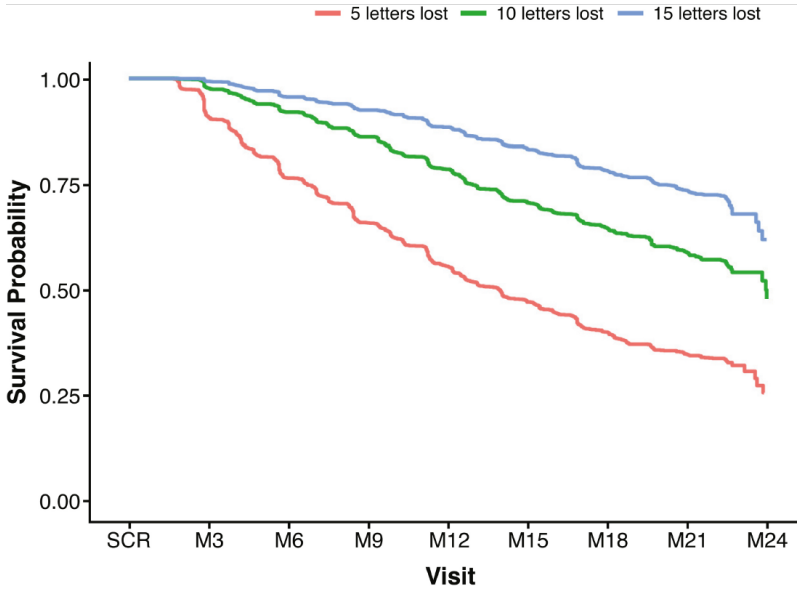
Visual Loss in Geographic Atrophy

Learnings from the Lampalizumab Trials

Neha Anegondi, MTech,[1] Verena Steffen, MSc,[1] Srinivas R. Sadda, MD,[2,3] Steffen Schmitz-Valckenberg, MD,[4,5] Adnan Tufail, MD,[6,7] Karl Csaky, MD, PhD,[8] Eleonora M. Lad, MD, PhD,[9] Peter K. Kaiser, MD, FASRS,[10] Daniela Ferrara, MD, PhD,[1] Usha Chakravarthy, FRCOphth, PhD[11]

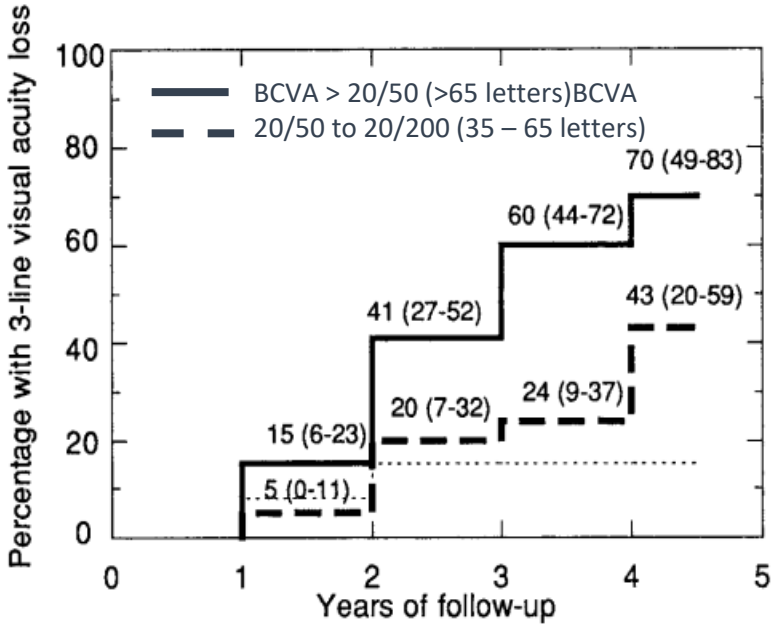


- >2000 eyes in the lampalizumab program
- Mean Baseline VA = 66 letters (~20/50)
- Mean Baseline GA Area = ~8.0 mm²
- ~25% had BCVA ≥15-LL at 2 years

Ophthalmology (2024)
https://doi.org/10.1016/j.ophtha.2024.11.017

Enlargement of Atrophy and Visual Acuity Loss in the Geographic Atrophy Form of Age-related Macular Degeneration

Janet S. Sunness, MD,[1,2] Joel Gonzalez–Baron, MD,[1] Carol A. Applegate, COT,[1] Neil M. Bressler, MD,[1–3] Yan Tian, BS,[3] Barbara Hawkins, PhD,[4] Yolanda Barron, MS,[4] Akiva Bergman, BTL[1]



- 123 GA patients; natural history study
- Median Baseline VA = 20/44
- Median Baseline GA Area 2.9 Disc Areas
- Vision Loss varied with BL VA, ~30% ≥15-LL at 2 years

Ophthalmology (1999)
doi:10.1016/S0161-6420(99)90340-8

In OAKS and DERBY, Mean Visual Acuity Declined from Baseline Through 24 Months in All Treatment Groups

THE LANCET

This journal Journals Publish Clinical Global health Multimedia Events About

ARTICLES · Volume 402, Issue 10411, P1434-1448, October 21, 2023

Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials

Jeffrey S Heier, MD [a,*] · Eleonora M Lad, MD [b,*] · Prof Frank G Holz, MD [c] · Prof Philip J Rosenfeld, MD [d] · Prof Robyn H Guymer, MBBS [e] · David Boyer, MD [f] · et al. Show more

- **Mean Baseline VA = ~59 letters (~20/63)**
- **Mean Baseline GA Area ~8.3 mm^2**

Lancet, Oct 2023
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01520-9/abstract

Least Squares Mean Change from Baseline, ETDRS letters

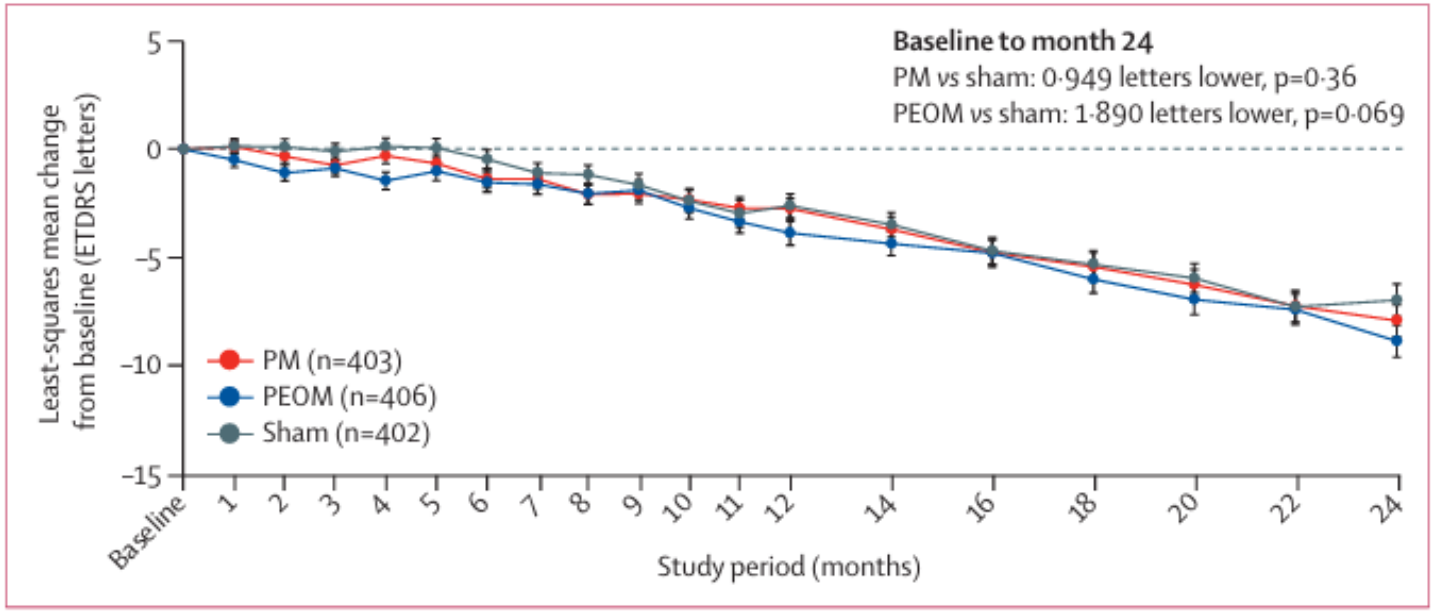


Figure 4: **Least-squares mean change in normal-luminance best-corrected visual acuity score in the study eye of participants of OAKS and DERBY combined**
Change from baseline to month 24 was measured on ETDRS charts. Error bars show SEs. ETDRS=Early Treatment Diabetic Retinopathy Study. PEOM=pegcetacoplan every other month. PM=pegcetacoplan monthly.

ARCHER: Phase 2 Trial Of The C1q Inhibitor ANX007 (Vonaprument) in Patients with Dry AMD and GA

Randomized, double-masked
Included **foveal and non-foveal** lesions
Stratified for lesion location and lesion size
12 months of Active Treatment (n=270)

Sham monthly or every other month (n=89)	Vonaprument 5mg monthly (EM) (n=89)	Vonaprument 5mg every other month (EOM) (n=92)

PRIMARY ENDPOINT

Rate of Change in GA lesion area as assessed by fundus autofluorescence at Month 12

PRESPECIFIED FUNCTIONAL ANALYSES

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

Off-treatment
(6 months)

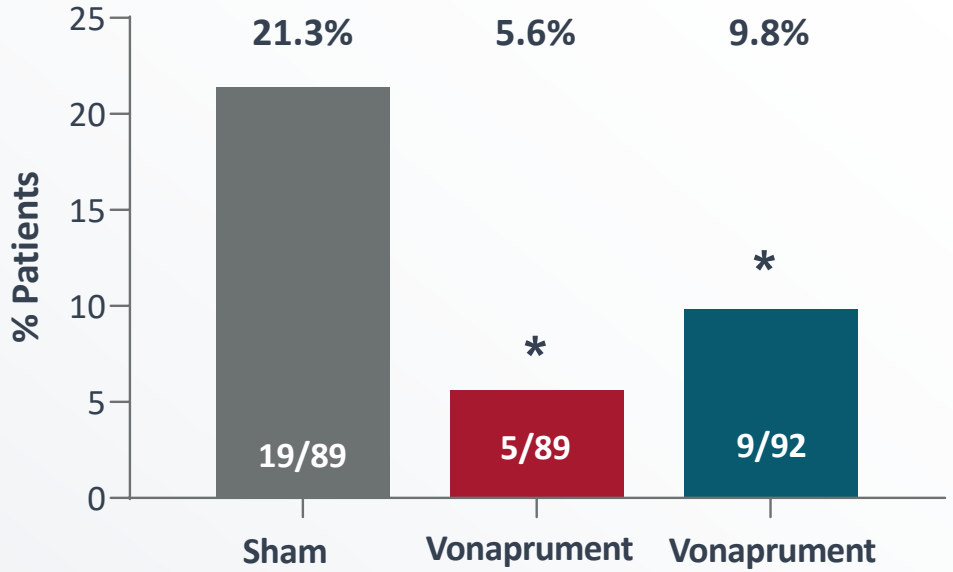
END OF STUDY
Month 18

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

CHARACTERISTIC	SHAM POOLED (N=89)	VONAPRUMENT EM (N=89)	VONAPRUMENT 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 (%)	86 (96.6%)	88 (98.9%)	89 (96.7%)
Mean BCVA, mean (SD)	**58.5 (16.2) ~20/70**	**58.8 (17.2) ~20/70**	**57.9 (15.3) ~20/70**
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%)

Fewer Vonaprument-Treated Eyes Experienced BCVA ≥15-Letter Loss Compared to Sham

PATIENTS WITH CONFIRMED BCVA ≥15-LETTER LOSS THROUGH MONTH 12 OR LAST VISIT#

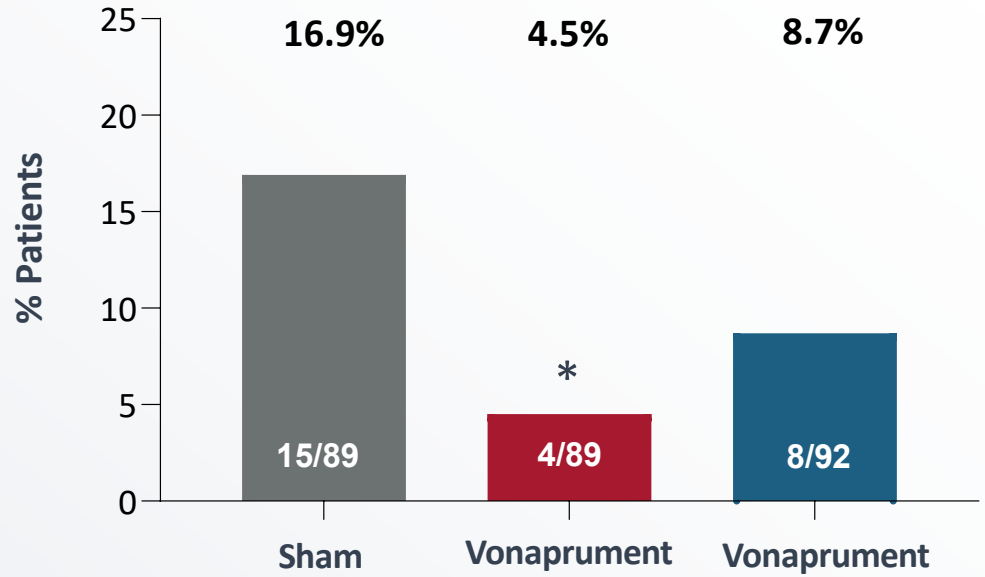


Nominal p-value vs Pooled Sham^	---	0.0021	0.032

#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

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

Month 12 event confirmed at Month 15



Nominal p-value vs Pooled Sham^	---	0.0076	0.0994

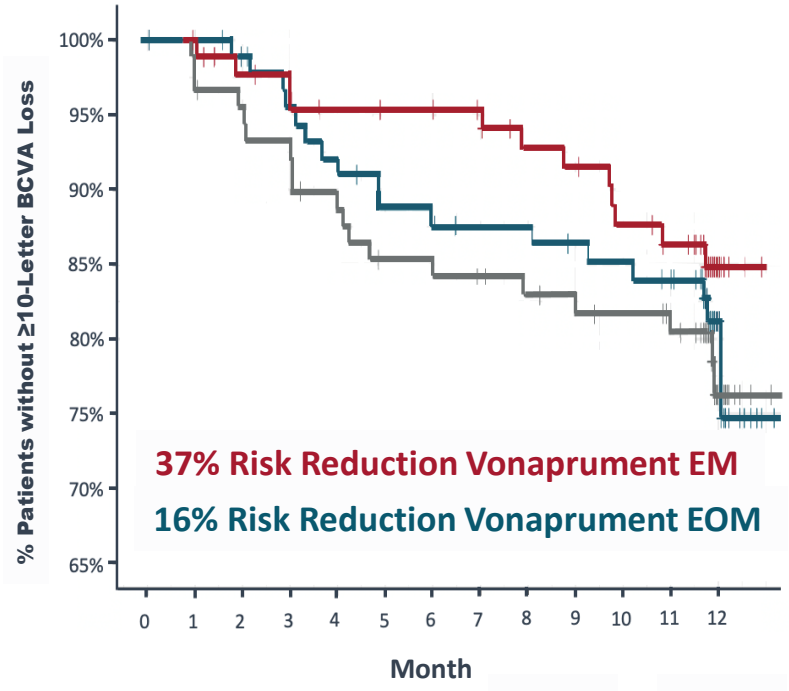
##Confirmed at two consecutive visits through month 12; month 12 event confirmed at month 15
^Nominal p-value from a Chi-square test in ITT population: *Nominal p < 0.05

Vonaprument, formerly ANX007

Visual Acuity Outcomes: BCVA ≥10-, ≥15- and ≥20-Letter Loss Through 12 Months

Persistent BCVA Vision Loss Through Month 12, Confirmed at Month 15

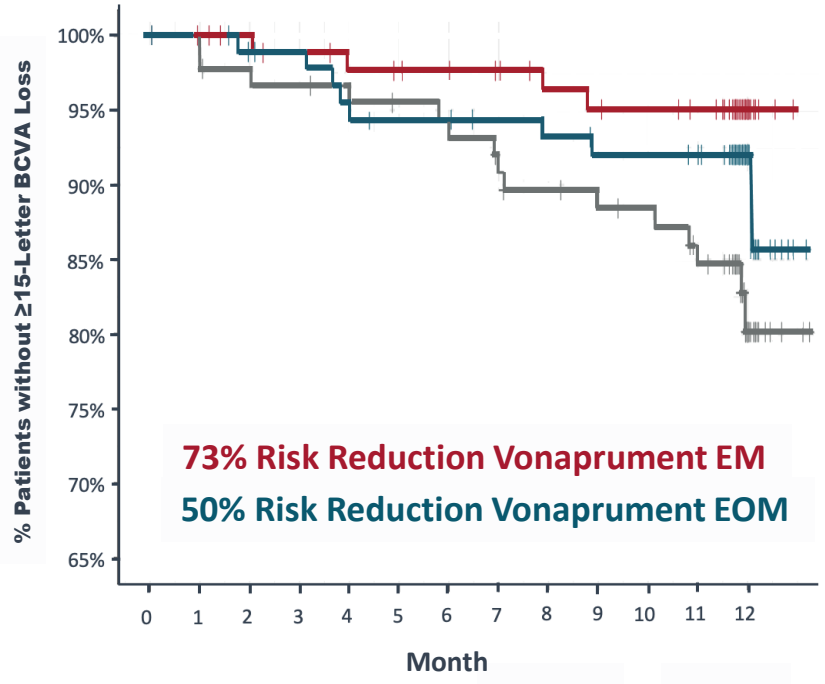
≥10-LETTER LOSS



37% Risk Reduction Vonaprument EM

16% Risk Reduction Vonaprument EOM

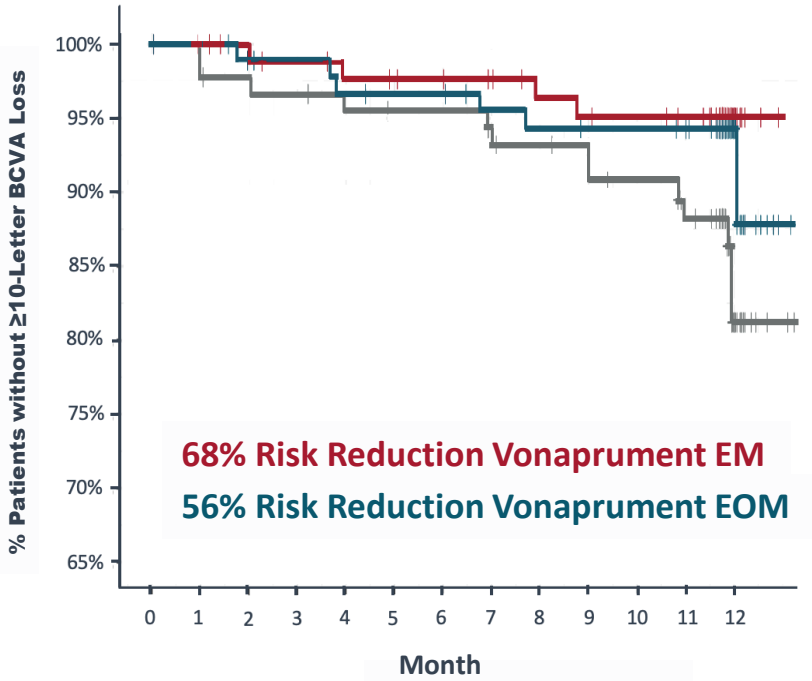
≥15-LETTER LOSS



73% Risk Reduction Vonaprument EM

50% Risk Reduction Vonaprument EOM

≥20-LETTER LOSS



68% Risk Reduction Vonaprument EM

56% Risk Reduction Vonaprument EOM

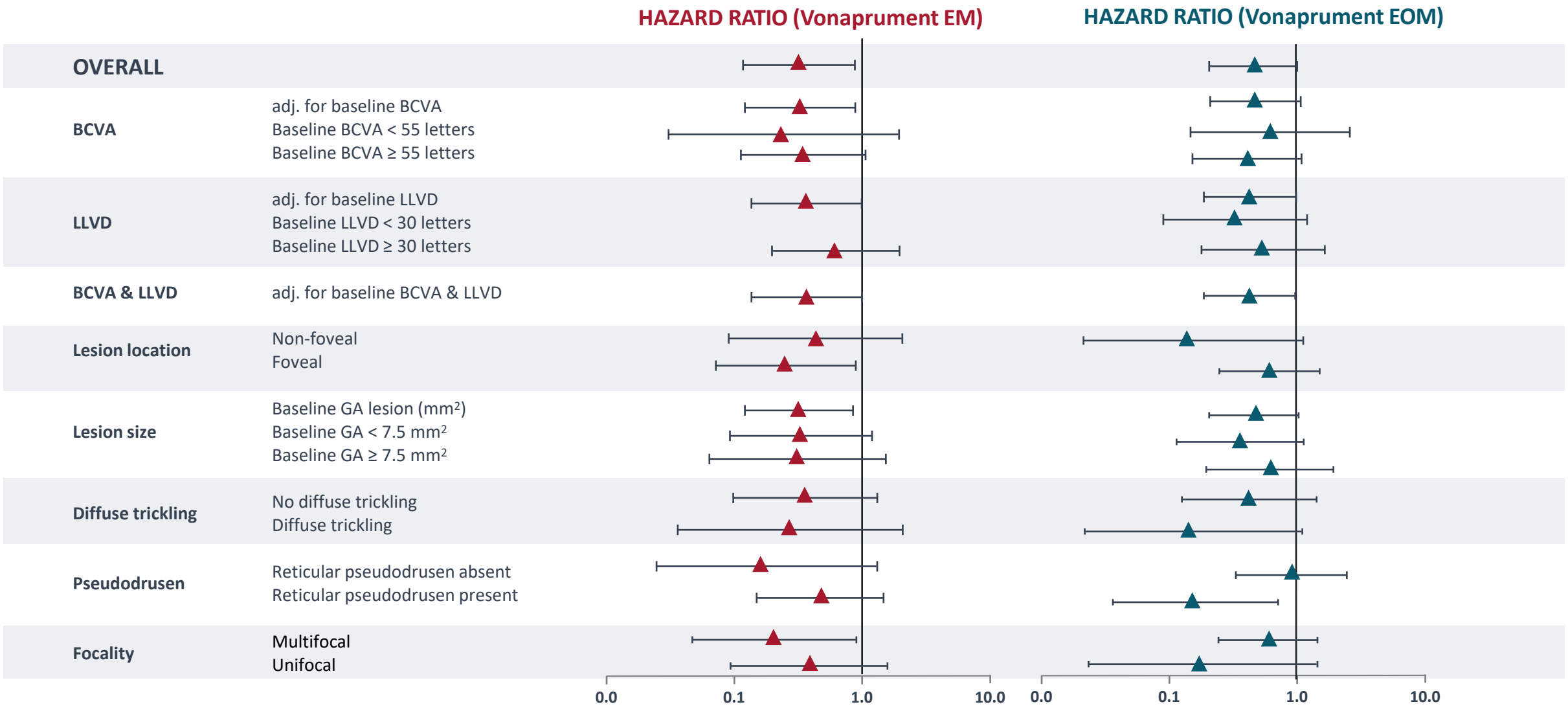
Nominal p-value vs sham^	≥10-LETTER LOSS		≥15-LETTER LOSS		≥20-LETTER LOSS	
	EM	EOM	EM	EOM	EM	EOM
	0.1952	0.6015	0.0119*	0.1098	0.0330*	0.0841

#Persistent for two consecutive visits through month 12; month 12 confirmed at month 15 visit

^Nominal p-value from a Chi-square test in ITT population

* P < 0.05

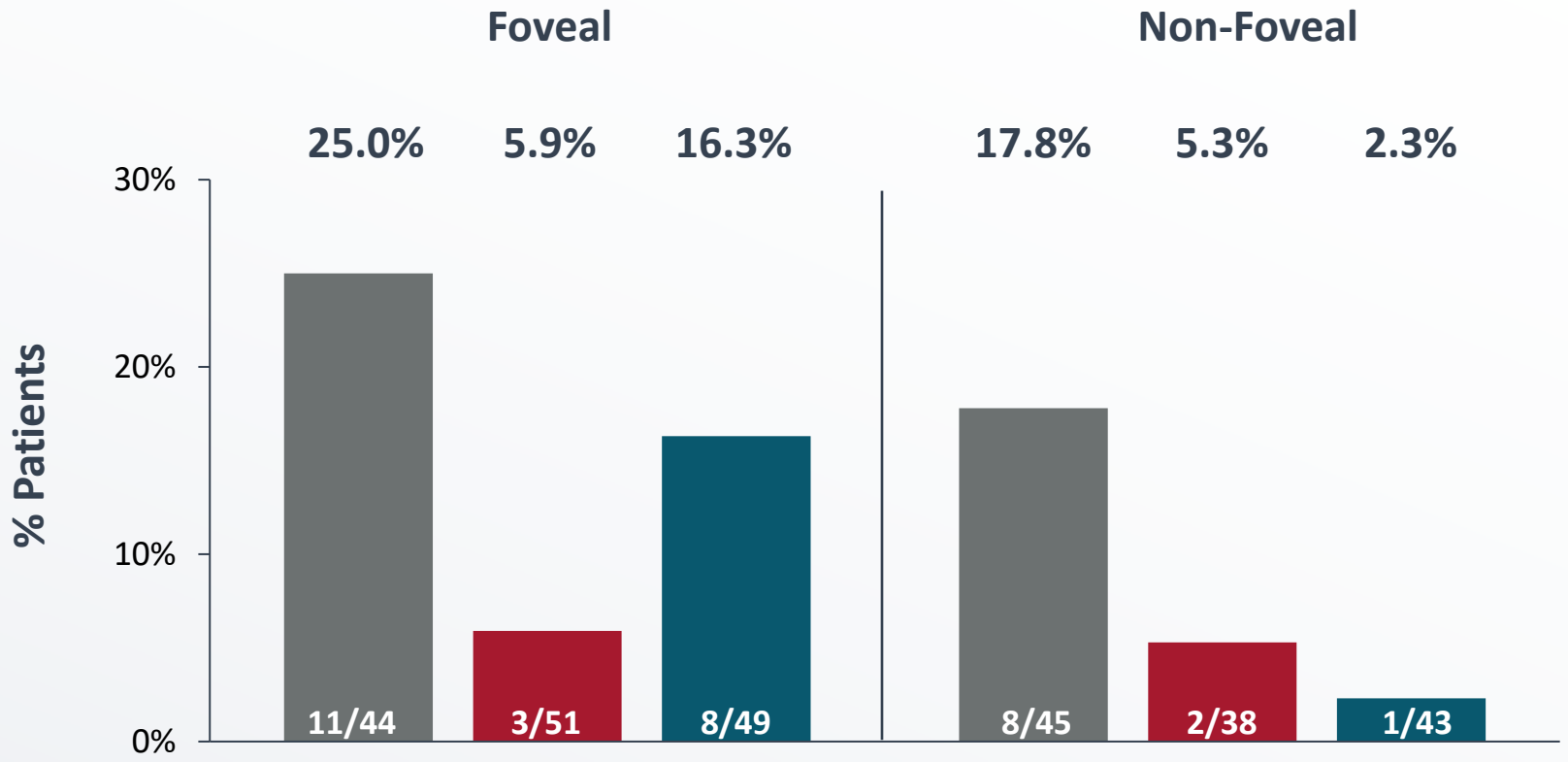
Protection of Vision Consistent Across Baseline Characteristics



*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 Vonaprument EM group for the subgroup.

Sub-Group Analysis: Visual Acuity Outcomes in Foveal vs. Non-Foveal Lesions

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

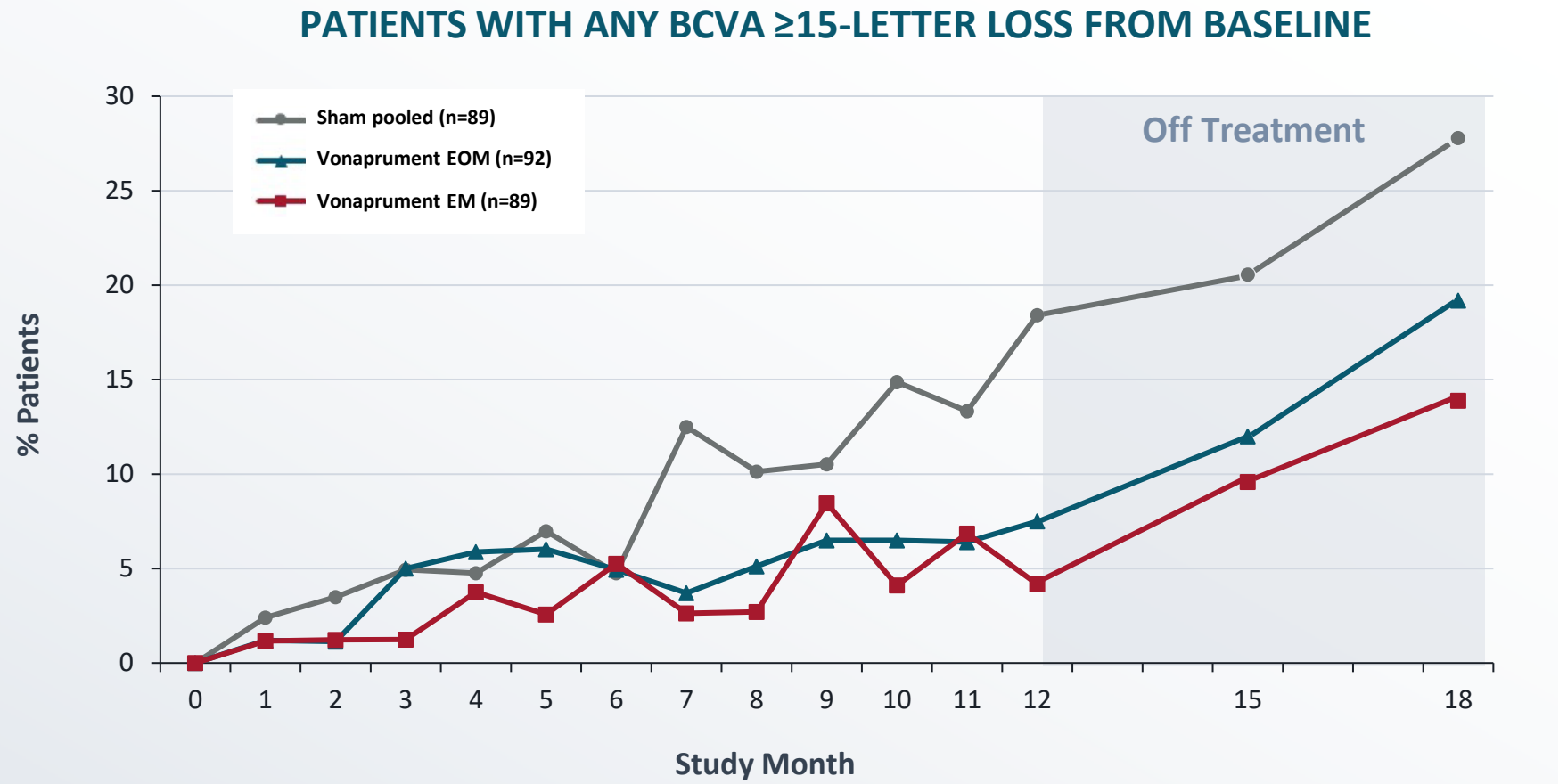


Nominal summary p-value vs. sham^	
Vonaprument EM (pooled)	0.0019
Vonaprument EOM (pooled)	0.0254

#Confirmed 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

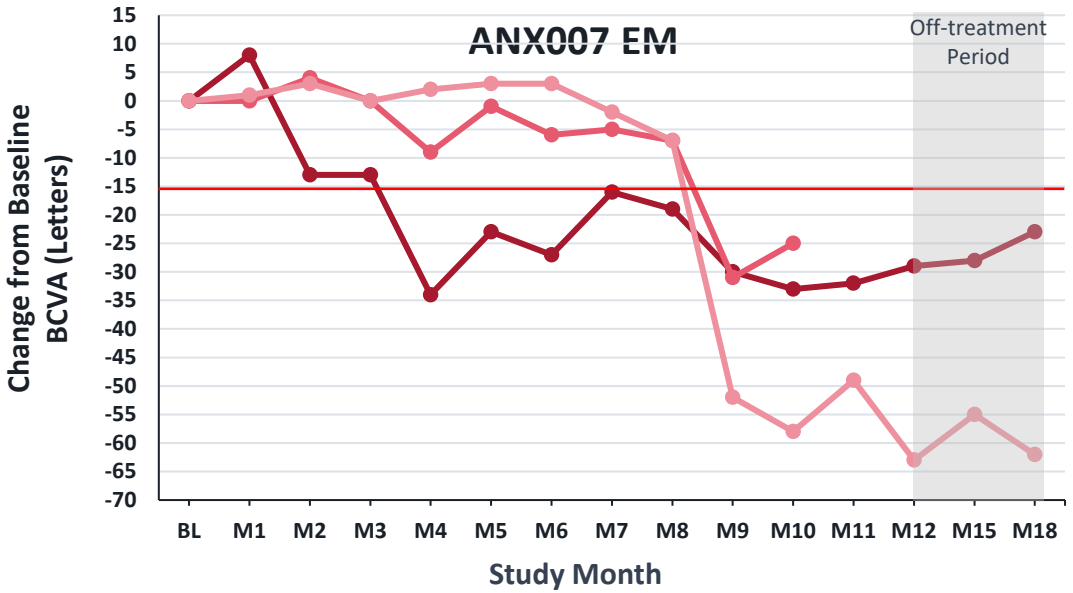
Proportion of Eyes With BCVA ≥15-Letter Loss Accelerated After Cessation of Treatment

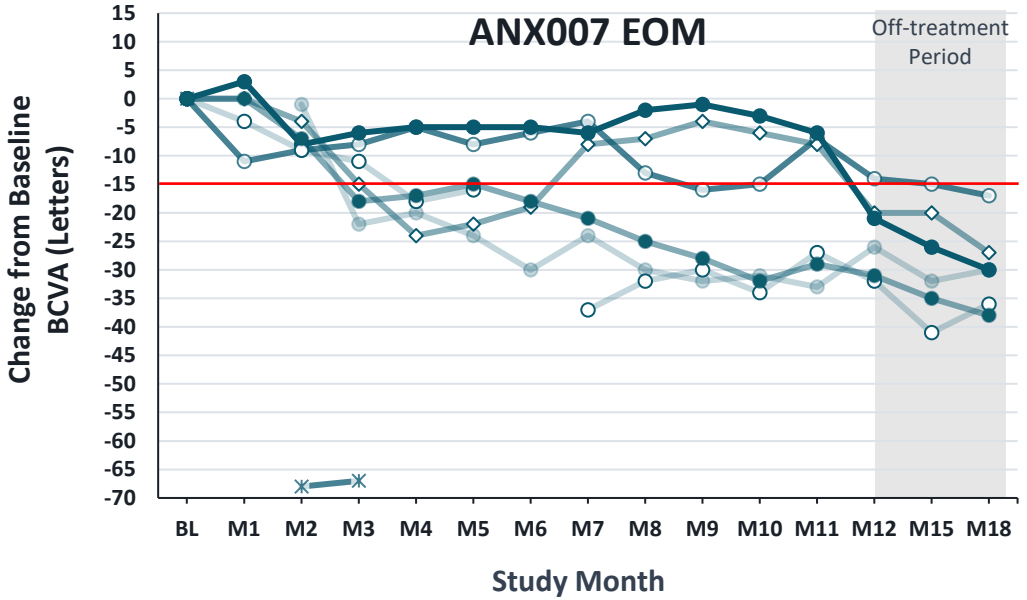
Consistent with true on-treatment drug effect and disease-modifying mechanism of action

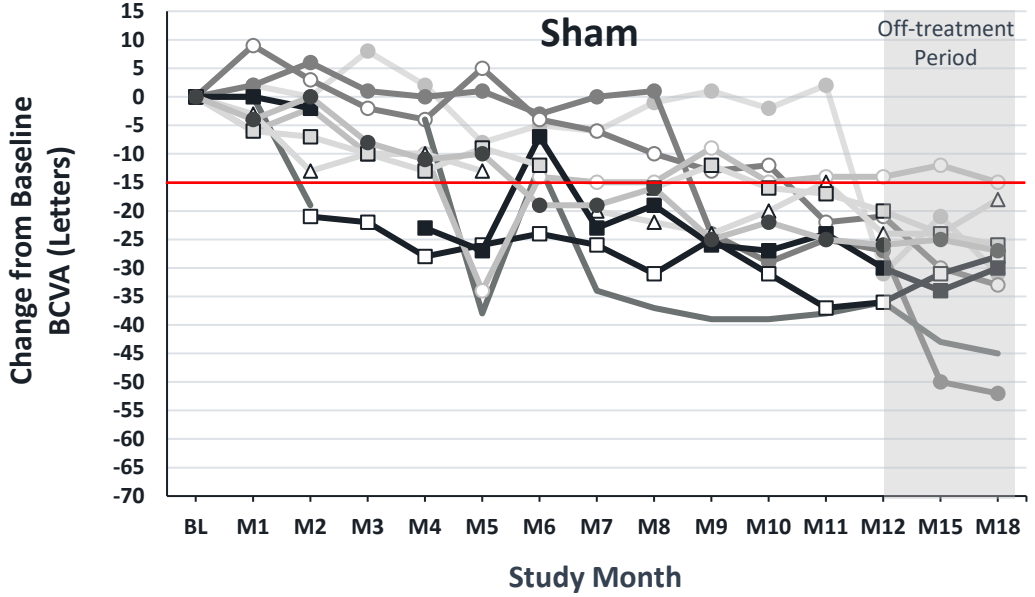


- Low frequency (<0.6% per month) of single BCVA ≥15-letter losses in EM- and EOM-treated groups during 12-month treatment period
- While benefit was maintained after treatment cessation the rate of BCVA≥15 LL increased to parallel that of sham (>1.6% per month)

Subgroup* Analysis: Change From Baseline Through Month 18 in the ARCHER Study: ≥15-Letter Loss Group







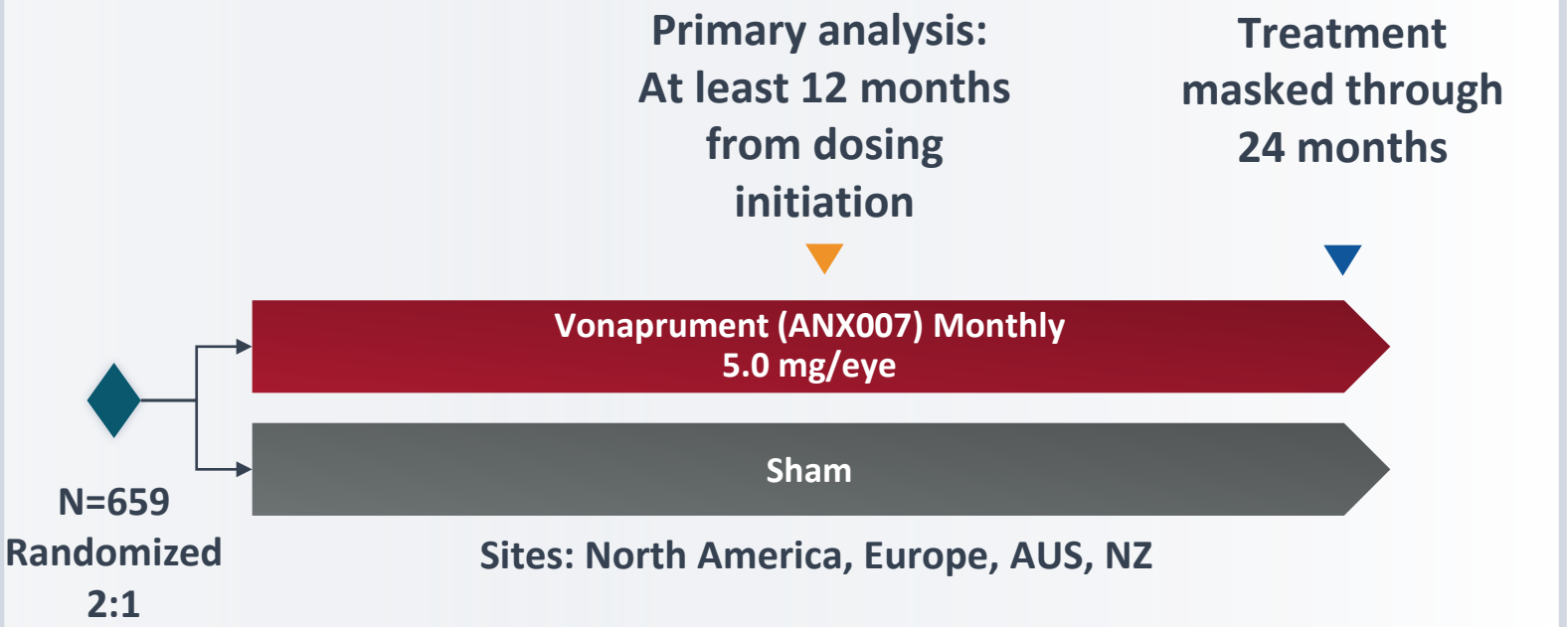
BCVA ≥15-LL Definition:
2 Consecutive Visits during the treatment period; Month 12 loss confirmed at Month 15

*Subgroup of patients in ARCHER meeting ARCHER II vision eligibility requirements

ARCHER II Phase 3 Program – Now Fully Enrolled

POPULATION FOR ARCHER II: Similar to ARCHER population, including foveal and non-foveal lesions and enriched for BCVA to exclude those with <45 ETDRS letters at baseline

PRIME designation from EMA



PRIMARY ENDPOINT

Persistent* BCVA ≥15-letter loss through primary analysis timepoint

** ≥15-letter loss confirmed at two consecutive visits*

SECONDARY ENDPOINTS

Safety, LLVA, EZ integrity

Key Take Home Messages

- Data from clinical trials indicate that a meaningful proportion of dry AMD patients with GA can lose 15 or more ETDRS letters over 1 to 2 years
- In ARCHER, through 12 months, fewer patients lost ≥15 letters with monthly vonaprument treatment compared to sham, with a risk reduction of 73%
  - These trends were seen across several measures of visual acuity
  - Trends were consistent across baseline characteristics and lesion phenotypes
- Assessing disease progression using functional parameters, such as visual acuity, is critical to determining therapeutic effect, as opposed to anatomical parameters alone