Clinical Rationale for Loss of 15 or More ETDRS Letters in Eyes with Dry AMD and GA: Analysis of the Phase 2 ARCHER Visual Acuity Outcomes

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INTRODUCTION

- Activation of the classical complement cascade has been implicated in the pathogenesis of geographic atrophy (GA) and other neurologic diseases
- C1q, the initiating molecule of the classical complement cascade, is a common driver of neurodegeneration
- Inhibition of C1q appears to convey neuroprotective effects across several neurodegenerative diseases
- Vonaprument is an antibody fragment that inhibits C1q and is delivered intravitreally
- The Phase 2 ARCHER study (NCT04656561) compared vonaprument (ANX007) 5mg monthly (EM), vonaprument (ANX007) 5mg every other month (EOM), or sham (EM or EOM)

BACKGROUND

Vision-Based Primary Endpoints in Ophthalmology

- BCVA measures – particularly 15-letter changes – have been one of the "standard" visual acuity measures in ophthalmological pivotal studies historically

APPROVED PRODUCT	FUNCTIONAL PRIMARY ENDPOINT
Wet AMD	
Lucentis®	Trial 1 and 2: BCVA ≥15-letter change Trial 3 and 4: Mean BCVA change
Eylea®/Eylea HD®	BCVA ≥15-letter change/Mean BCVA change
Vabysmo®	Mean BCVA change
DME	
Lucentis®	BCVA ≥15-letter change
Eylea®/Eylea HD®	Mean BCVA change
Vabysmo®	Mean BCVA change
Iluvien®	BCVA ≥15-letter change
Ozurdex®	BCVA ≥15-letter change
GA	
No Approved Vision-Preserving Treatments	

What is 15-Letter Loss?

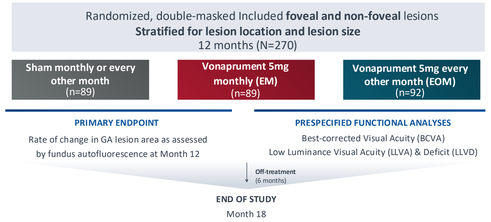
- Decline of 15 or more in BCVA letter score is relevant in GA because the measure represents:
  - 1) a Snellen equivalent of 3 line or greater loss on a standardized ETDRS chart
  - 2) a doubling (or more) of the visual angle
  - 3) a 0.3 or more logMAR change
  - 4) vision decline (for example):
    - 20/40 to 20/80 or worse
    - 20/63 to 20/125 or worse, etc.

Other similar cohorts demonstrate ~25-35% of patients with BCVA ≥15-letter loss at two years[1,2,3]

- Loss of 15 or more ETDRS letters as measured by BCVA was a prespecified analysis in ARCHER (loss events defined as occurring at two consecutive study visits, including month 12)

ARCHER METHODS & RESULTS

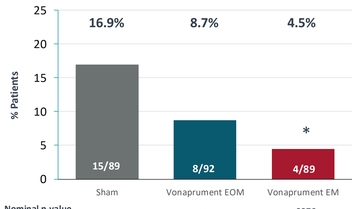
ARCHER Phase 2 Study Design



- 6.2% greater reduction in rate of change in retinal pigment epithelium (RPE) loss from baseline with vonaprument treatment at 12 months – did not reach statistical significance (primary)
- Consistent treatment effects observed across visual acuity measures (BCVA, LLVA) support effect of vonaprument in GA
- Preservation of photoreceptor (EZ) structure across the full macular grid and subdomains is supportive of vonaprument vision impact

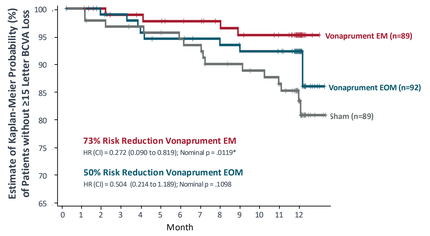
ARCHER RESULTS

Proportion of Patients With ≥15-letter BCVA Loss



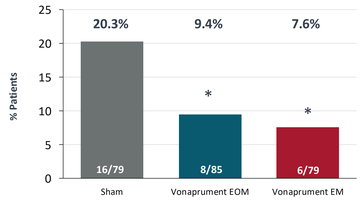
Confirmed at two consecutive visits through month 12 (month 12 supported by month 15 visit)
^Nominal p-value from a Chi-square test in ITT population: *Nominal p < .05

Proportion of Patients Without ≥15-letter BCVA Loss at 2 Consecutive Visits Through Month 12



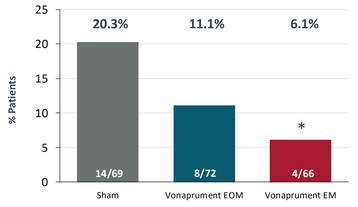
HR, hazard ratio; Nominal log-rank test (versus sham) p-values are presented;
*Confirmed BCVA 15-LL at two consecutive visits including month 12 supported by month 15 visit
Nominal p-value from a Chi-squared test in ITT population; *Nominal p < .05

Proportion of Patients With ≥15-letter LLVA Loss



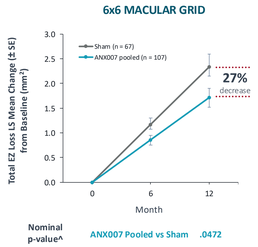
Patients with at least one post-baseline LLVA measurement and two consecutive or last visit 15-letter loss events; ^Nominal p-value from a Chi Square test; *Nominal p < .05

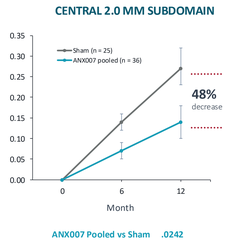
Proportion of Patients With ≥15-letter BCVA Loss in Subpopulation Meeting ARCHER II Baseline BCVA Criterion



Confirmed at two consecutive visits through month 12 (month 12 supported by month 15 visit) in ITT population excluding patients with baseline BCVA <45; : *Nominal p < .05

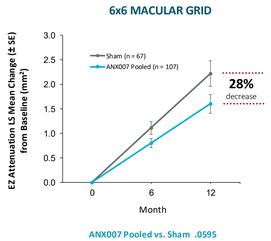
LS Mean Change from Baseline in Total Ellipsoid Zone (EZ) Loss Through 12 Months





Nominal p-value^ ANX007 Pooled vs Sham .0472 | ANX007 Pooled vs Sham .0242

LS Mean Change from Baseline in EZ Attenuation (< 20 µm) Through 12 Months

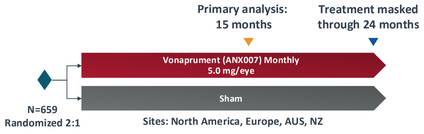


ANX007 Pooled vs. Sham .0595

^Nominal p-values from a linear mixed model for repeated measures model (slope) analysis;
Heidelberg Spectralis OCT population with baseline and at least one post-baseline OCT image, excludes patients with >98% atrophy/attenuation at baseline

ARCHER II PHASE 3 PROGRAM

ARCHER II Design



Fast Track designation (FDA)

PRIME designation (EMA)*

*Also selected by EMA for Product Development Coordinator program

- Primary endpoint: Proportion of eyes with confirmed BCVA ≥15-letter loss through primary analysis timepoint
  - Confirmed defined as ≥15-letter loss confirmed at two consecutive visits
- Secondary endpoints: Safety, LLVA, LLVD, EZ integrity
- Study Population: Comparable to ARCHER; foveal and non-foveal lesions included; history of CNV in fellow eye permitted; eyes with <45 BCVA letters at baseline are excluded
- ARCHER II is fully enrolled; data expected 4Q 2026

REFERENCES

1. Anegondi N, Steffen V, Sadda SR, Schmitz-Valckenberg S, Tufail A, Csaky K, Lad EM, Kaiser PK, Ferrara D, Chakravarthy U. *Visual Loss in Geographic Atrophy: Learnings From the Lampalizumab Trials*, Ophthalmology. 2025 Apr; 132(4):420-430. doi: 10.1016/j.ophtha.2024.11.017
2. Schmitz-Valckenberg S, Nadal J, Fimmers R, Lindner M, Holz F, Schmid M, Fleckenstein M. *Modeling Visual Acuity In Geographic Atrophy Secondary to Age-Related Macular Degeneration*, Ophthalmologica. 2016; 235(4):215-24. doi: 10.1159/000445217
3. Sunness JS, Gonzalez-Baron J, Applegate CA, Bressler NM, Tian Y, Hawkins B, Barron Y, Bergman A. *Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration,* Ophthalmology. 1999 Sep;106(9):1768-79. doi: 10.1016/S0161-6420(99)90340-8

CONCLUSIONS

- ARCHER results suggest that C1q inhibition with vonaprument conveys a drug-related photoreceptor protective effect that may explain associated prevention of visual acuity loss
- ARCHER BCVA ≥15-letter loss incidence rate consistent with larger prior datasets
- Enrichment strategy in ARCHER II likely increases BCVA ≥15-letter loss incidence rate
- Data from inhibition with C1q suggest that the anti-C1q approach may provide neuroprotection against inflammation and neuronal damage and loss induced by downstream complement components
- Vonaprument has the potential to be the first pharmacologic treatment to preserve vision in patients with GA

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