Microglia-Induced Neuronal Injury Attenuation with C1q Inhibition: Outcomes in Geographic Atrophy and Huntington's Disease

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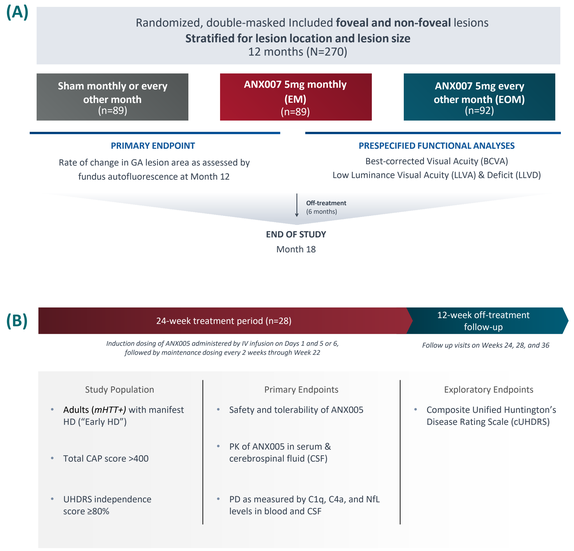
INTRODUCTION

- Activation of the classical complement cascade has been implicated in the pathogenesis of geographic atrophy (GA), Huntington's disease (HD), and other neurologic diseases
- C1q, the initiating molecule of the classical complement cascade, is a common driver of neurodegeneration in both the central nervous system (CNS) and peripheral nervous system (PNS) Inhibition of C1q appears to convey neuroprotective effects across several neurodegenerative diseases
- The Phase 2 ARCHER study (NCT04656561) compared ANX007 5mg monthly (EM), ANX007 5mg every other month (EOM), or sham EM or EOM **(Figure 1A)**
- The Phase 2 ANX005-HD-01 (NCT04514367) assessed ANX005 in patients who had, or were at risk for, manifest HD **(Figure 1B)**
  - ANX005 was generally well-tolerated, with a favorable benefit-to-risk profile in patients with HD[2]
  - Full C1q inhibition was maintained in the body & CNS through the on-treatment and into the off-treatment periods
- Thie current analysis aims to explore the relationship between preservation of visual acuity and reduction in ellipsoid zone (EZ) loss in GA and to evaluate outcomes in HD to better understand the role of C1q inhibition in neuroprotection against loss of neuronal synapses across these neurodegenerative diseases

Figure 1. Study Design: (A) ANX007 ARCHER and (B) ANX005-HD-01

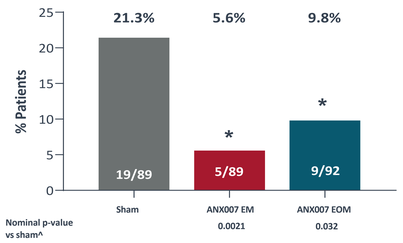


METHODS & RESULTS

- In ARCHER, 270 patients with dry AMD and GA were randomized to receive intravitreal (IVT) ANX007 5 mg EM, ANX007 5 mg EOM, or EM or EOM
  - The EM group achieved a 6.2% greater reduction in retinal pigment epithelium (RPE) from baseline compared to sham at 12 months (primary endpoint, as assessed by an independent reading center) which did not achieve statistical significance
- Outcomes assessed included:
  - Proportion of patients with 15-letter loss in best-corrected visual acuity (BCVA) at 2 consecutive visits through Month 12 **(Figure 2)**
  - Least squares (LS) mean change from baseline in ellipsoid zone (EZ) loss through Month 12 **(Figure 3)**
  - Proportion of patients without 15-letter loss in BCVA through Month 12 **(Figure 4)**
  - LS mean change from baseline in RPE through Month 12 **(Figure 5)**
- In ANX005-HD-01, eligible patients (CAP >400, Independence ≥80%) received induction dosing of ANX005 administered by IV infusion on Days 1 and 5 or 6, followed by maintenance dosing every 2 weeks through Week 22, with follow-up visits on Weeks 24, 28, and 36
- Outcomes assessed included:
  - Objectives of clinical efficacy, composite Unified Huntington's Disease Rating Scale (cUHDRS) and Total Functional Capacity (TFC) **(Figure 6)**

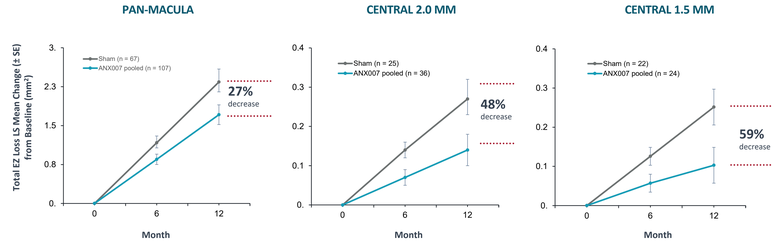
RESULTS

Figure 2. Proportion of Patients with 15-letter BCVA loss



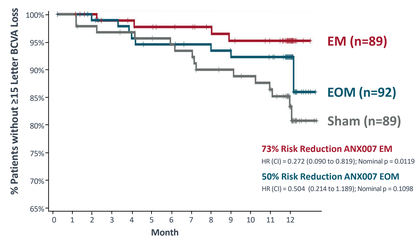
[#]Persistent for two consecutive visits through month 12 or at last study visit
^Nominal p-value from a Chi-square test in ITT population: * Nominal p < 0.05
Number Needed to Treat = 1 / (21.3 – 5.6) * 100= 6.4

Figure 3. Mean Change from Baseline in Total Ellipsoid Zone Loss Through 12 Months



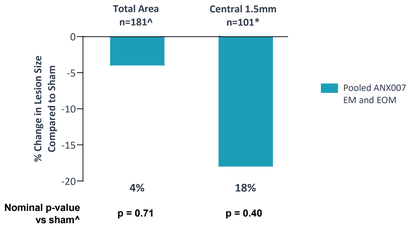
^Nominal p-values from a linear mixed model for repeated measures model (slope) analysis;
Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy/attenuation at baseline

Figure 4. Proportion of Patients Without ≥15-letter BCVA Loss at 2 Consecutive Visits Through Month 12



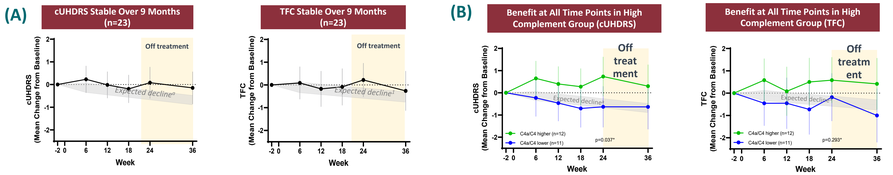
HR, hazard ratio; Nominal log-rank test (versus sham) p-values are presented;
[#]Persistent BCVA 15-LL at two consecutive visits including month 12 supported by ensuing (off-treatment) visit (Note difference in definition of persistent loss of vision compared to Figure 2)

Figure 5. LS Mean Change from Baseline in RPE in the Pooled ANX007 Group Versus Sham Through Month 12



[#]From a mixed model for repeated measures (MMRM) analysis; ^ITT population
*Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy at baseline

Figure 6. Mean Change from Baseline in cUHDRS and TFC in (A) Overall Population and (B) Patients with Higher Baseline Complement Activity



MMRM; LS means +/- 95% CI
[#]Expected decline = interpolated natural history from Schobel 2017 (TRACK-HD)

*Comparing higher vs lower C4a/C4 groups at week 2; MMRM; LS means +/- 95% CI; N=23.
[#]Expected decline = interpolated natural history from Schobel 2017 (TRACK-HD).
UHDRS = Unified Huntington's Disease Rating Scale; a clinical rating scale to assess four domains of clinical performance and capacity in HD
TFC = Total Functional Capacity; used to evaluate functional impairments across several domains in HD

CONCLUSIONS

- ARCHER results suggest that inhibition of C1q with ANX007 conveys a drug-related photoreceptor protective effect that may explain the associated prevention of VA loss
- In HD, activation of the classical complement pathway is initiated by C1q binding to substrate on neurons, ultimately leading to microglia-induced neuronal injury and loss
- In GA and HD, inhibition with C1q conveys neuroprotective effects, suggesting the anti-C1q therapy may provide neuroprotection against inflammation and neuronal damage and loss induced by downstream complement components

REFERENCES

1. Lad E et al. *C1q inhibition attenuates microglia-induced neuronal injury: Implications for GA and neurodegenerative diseases,* Macula Society 2025, Charlotte Harbor, FL.
2. Data on file

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