C1q inhibition attenuates microglia-induced neuronal injury: Implications for GA and neurodegenerative diseases

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Relevant Disclosures

Professor Stanga is a consultant to, and an investigator for, Annexon

Targeting C1q-Mediated Neurodegeneration – Preservation of Synapses and 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]

- Alzheimer's disease
- Amyotrophic Lateral Sclerosis
- Frontotemporal dementia
- Geographic Atrophy
- Glaucoma
- Guillain-Barré Syndrome
- Huntington's disease
- Retinal ischemia
- Schizophrenia
- Spinal muscular atrophy
- Traumatic brain injury

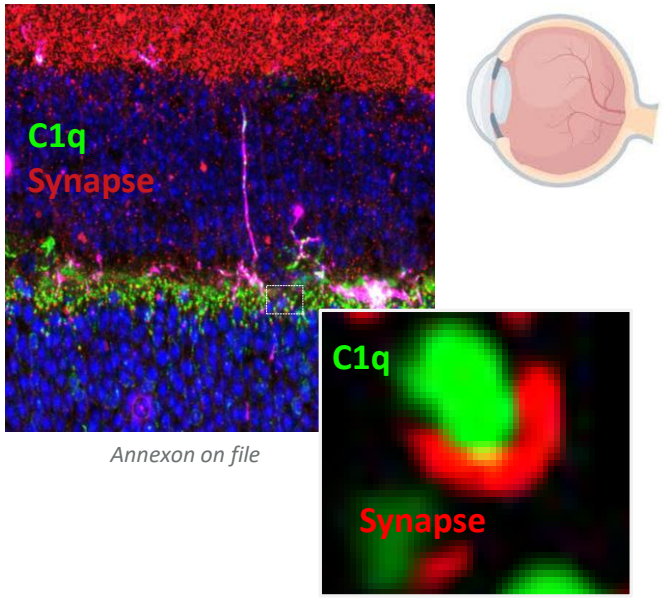
[1]Stevens, et al., 2007 DOI 10.1016/j.cell.2007.10.036; Schafer et al., 2012 DOI 10.1016/j.neuron.2012.03.026; Hong, et al., 2016 doi: 10.1126/science.aad8373; Lui et al., 2016 doi.org/10.1016/j.cell.2016.04.001; [2]Yednock, et al, 2022, doi.org/10.1186/s40942-022-00431-y

C1q is A Common Driver of Neurodegeneration in Both the Central and Peripheral Nervous System

C1q directly binds to synapses on stressed neurons, triggering elimination

C1q targeting synapses for elimination in the retina[1]

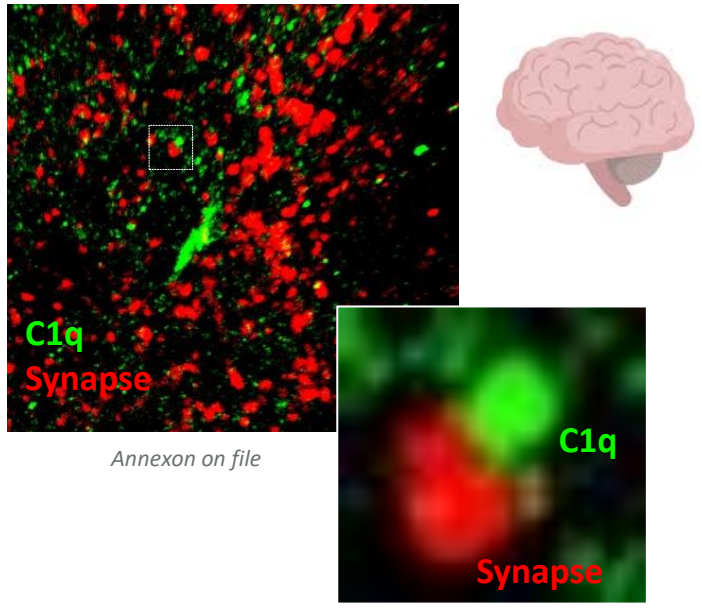
MODEL OF PHOTORECEPTOR DEGENERATION



Annexon on file

C1q targeting synapses for elimination in the brain[2]

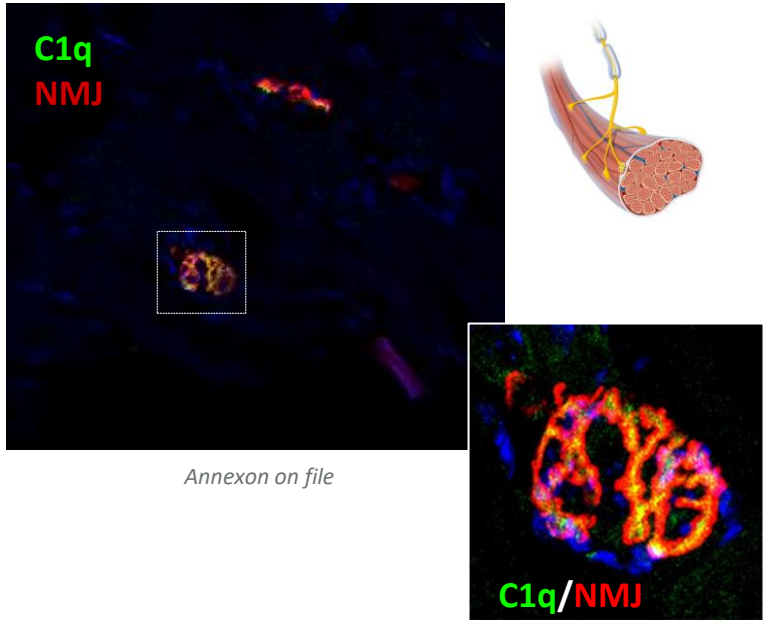
MODEL OF HUNTINGTON'S DISEASE



Annexon on file

C1q targeting neuromuscular junction (NMJ) for elimination in the PNS[3]

MODEL OF AMYOTROPHIC LATERAL SCLEROSIS



Annexon on file

C1Q INHIBITION PROTECTS AGAINST SYNAPSE LOSS AND NEURODEGENERATION IN SEVERAL DISEASE MODELS[4]

[1]Stevens, et al., 2007 DOI 10.1016/j.cell.2007.10.036; [2]Wilton, et al., 2023, doi: 10.1038/s41591-023-02566-3; [3]Idriss, et al., 2016 doi: 10.1186/s12974-016-0538-2
[4]Yednock, et al, 2022, doi.org/10.1186/s40942-022-00431-y

C1q Inhibition in Huntington’s Disease (HD)

Phase 2 Open-Label Clinical Trial of Tanruprubart (ANX005) in Patients With or At Risk of Huntington's Disease (HD)

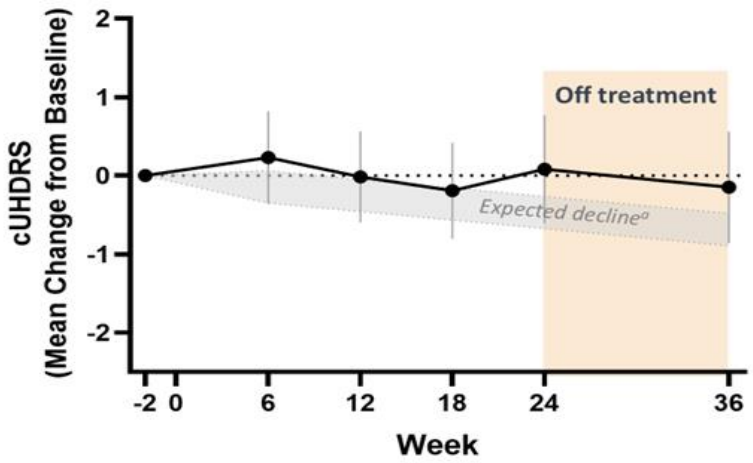
Study Design:

24-week treatment period (n=28) → 12-week off-treatment follow-up

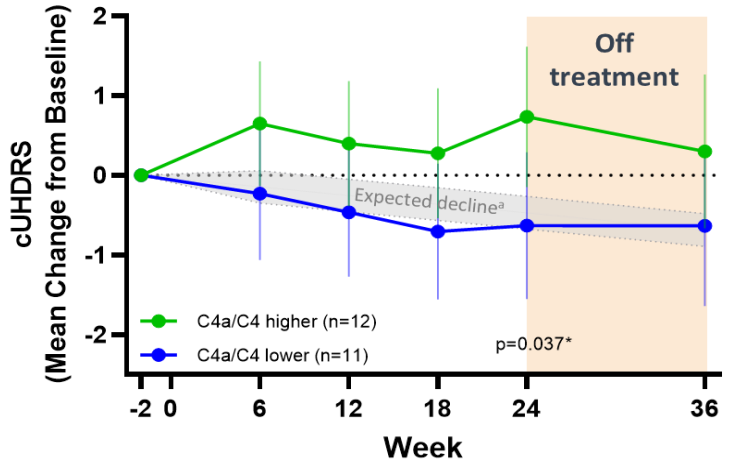
Induction dosing of ANX005 administered by IV infusion on Days 1 and 5 or 6, followed by maintenance dosing every 2 weeks through Week 22

Follow up visits on Weeks 24, 28, and 36

Overall Population (n=23): cHUDRS Stable Over 9 Months



High Complement Activity at Baseline (n=12): cHURDS Reflects Treatment Benefit at All Time Points



MMRM; LS means +/- 95% CI

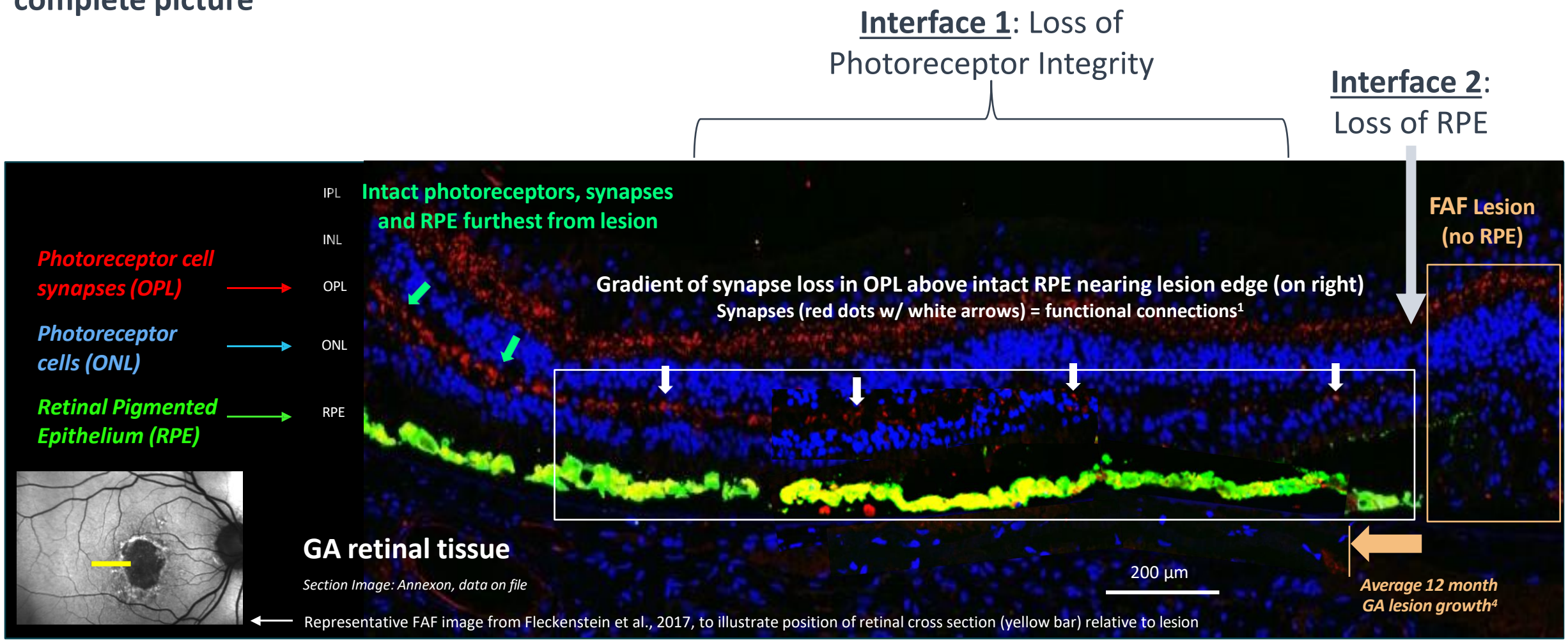
[a] Expected decline = interpolated natural history from Schobel 2017 (TRACK-HD)

UHDRS = Unified Huntington's Disease Rating Scale; a clinical rating scale to assess four domains of clinical performance and capacity in HD; C4a and C4 levels are indicators of immune system activation and inflammation

C1q Inhibition in Dry AMD and GA

Two Structural Disease Interfaces in Advanced Dry AMD

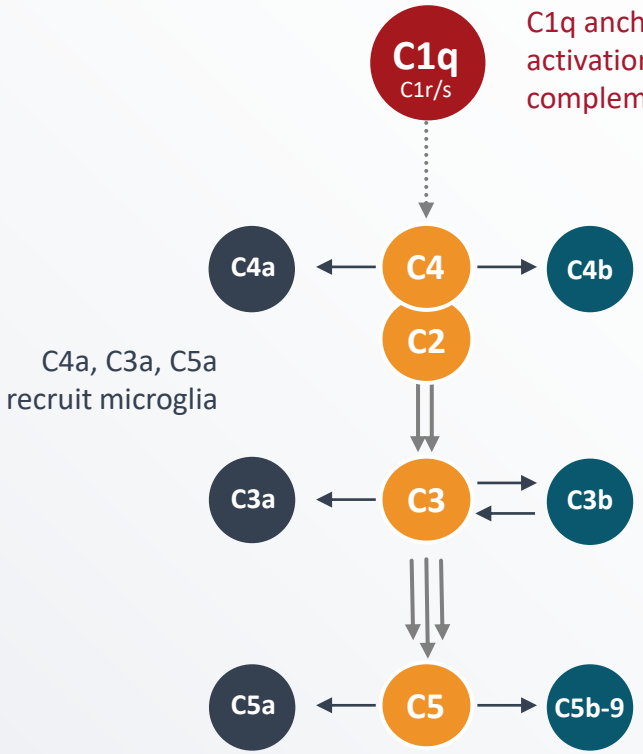
Monitoring RPE alone provides incomplete view of disease; assess photoreceptors and function for complete picture



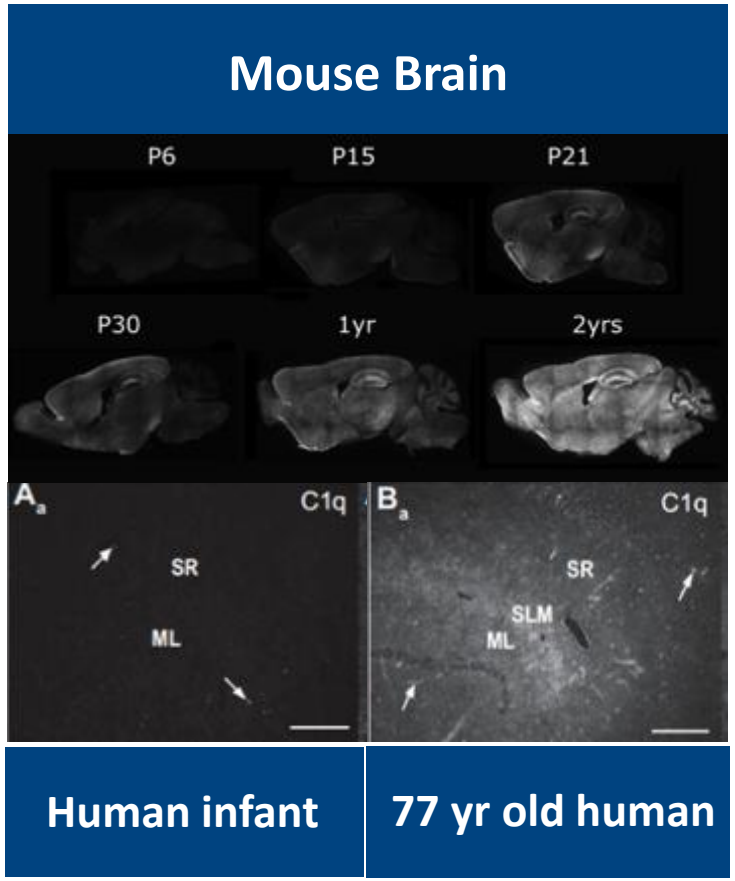
[1]Selkoe, 2002 doi: 10.1126/science.1074069; Burger, et al., doi.org/10.1016/j.ydbio.2021.04.001; [2]Bird et al., 2014 *JAMA Ophthalmol* doi:10.1001/jamaophthalmol.2013.5799; Li, et al., 2018 *Retina* 38:1937; Pfau, et al., 2020 10.1001/jamaophthalmol.2020.2914; Sarks, et al., 1988 *Eye* 2:552; [3]Heier, et al., 2020 Ophthalmology Retina **4**:673; [4]Shen, et al., 2020 *Ophthalmol Retina* **4**:899

Expression of C1q, A Critical Driver of Synapse Removal Across the CNS, Increases With Aging

Classical Complement Cascade Uniquely Responsible for Neuroinflammation and Synapse Removal

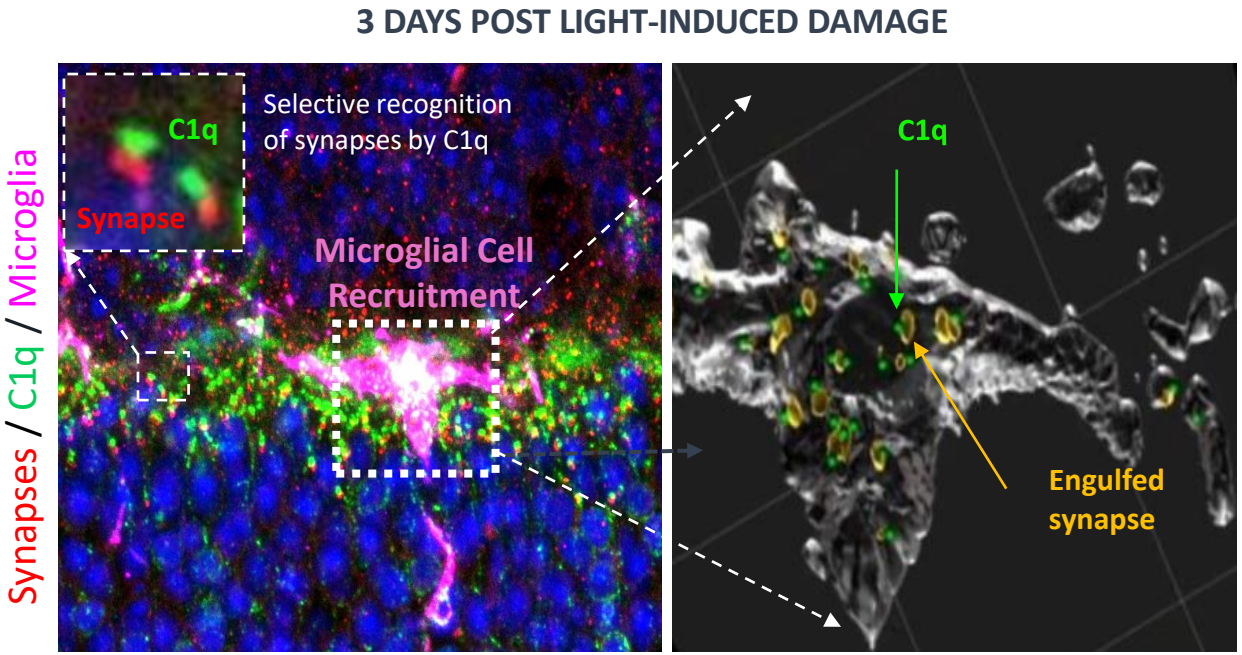


C1q Expression Increased with Aging in CNS: Rodents and Humans



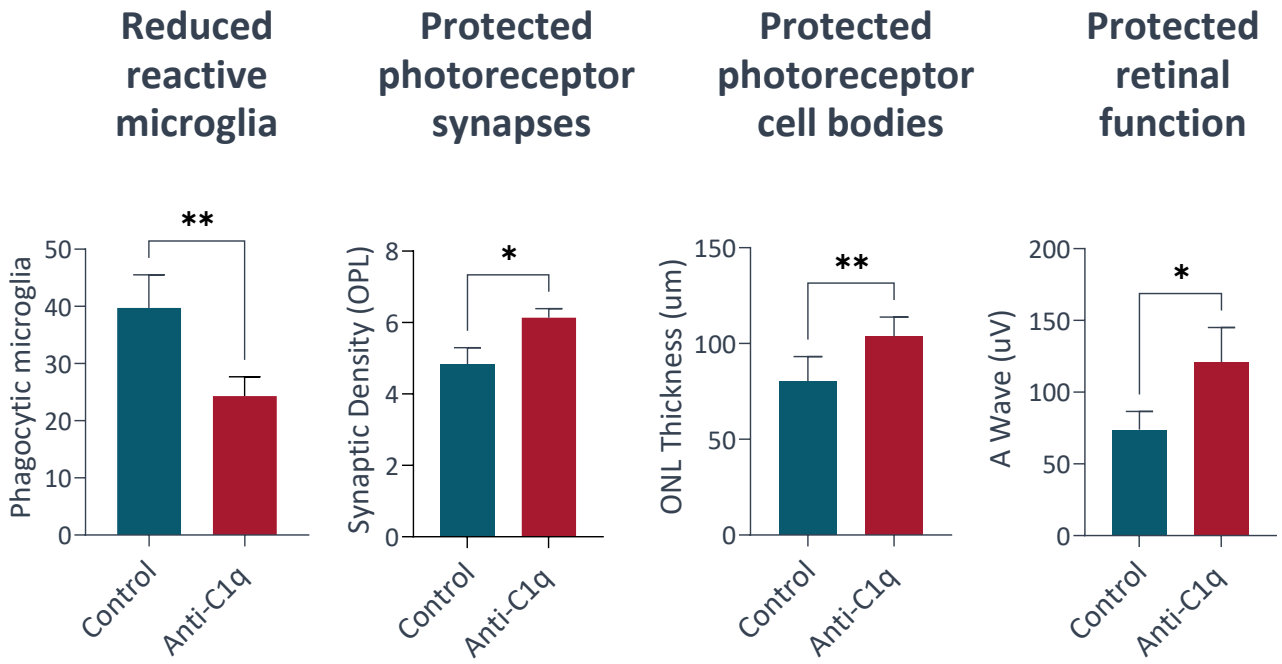
C1q-Driven Neuroinflammation Results in Photoreceptor Loss in An Animal Model

Upon Photoreceptor Damage in a Rodent Model, Microglia Engulf C1q-Coated Synapses



Tassoni, et al., ARVO, 2024 and Annexon on file
Synapses (presynaptic / bassoon, red)
C1q (green)
Microglia (Iba1, magenta)
DAPI (nuclei, blue)

C1q inhibition reduced reactive microglia, synapse loss, & photoreceptor loss, and protected function



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

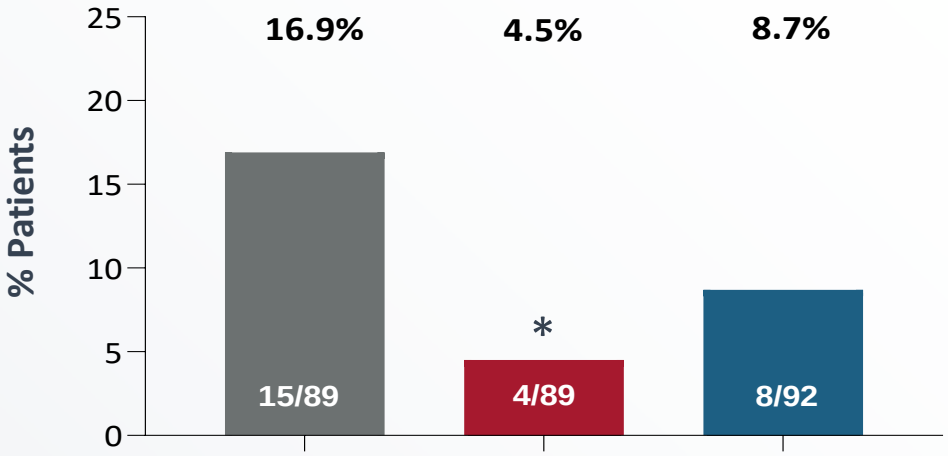
Best Corrected Visual Acuity (BCVA)
Low Luminance Visual Acuity (LLVA) & Deficit (LLVD)

Off-treatment
(6 months)

END OF STUDY
Month 18

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

PROPORTION OF PATIENTS WITH CONFIRMED BCVA ≥15-LETTER LOSS AT TWO CONSECUTIVE VISITS THROUGH MONTH 12*

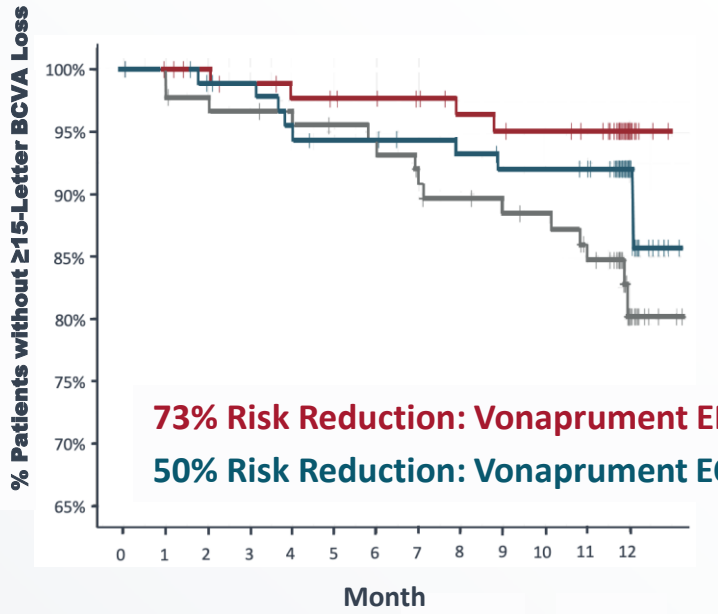


Nominal p-value vs Pooled Sham^	---	Vonaprument EM 0.0076	Vonaprument EOM 0.0994

*BCVA ≥15-Letter Loss at Month 12 was confirmed at the subsequent visit (Month 15). In ARCHER, visits were monthly through Month 12 and then at Months 15 & 18

^Nominal p-value from a Chi-square test in ITT population: *Nominal p < 0.05

PROBABILITY OF CONFIRMED## BCVA ≥15-LETTER LOSS THROUGH MONTH 12



Nominal p-value vs sham^	EM	EOM
	0.0119*	0.1098

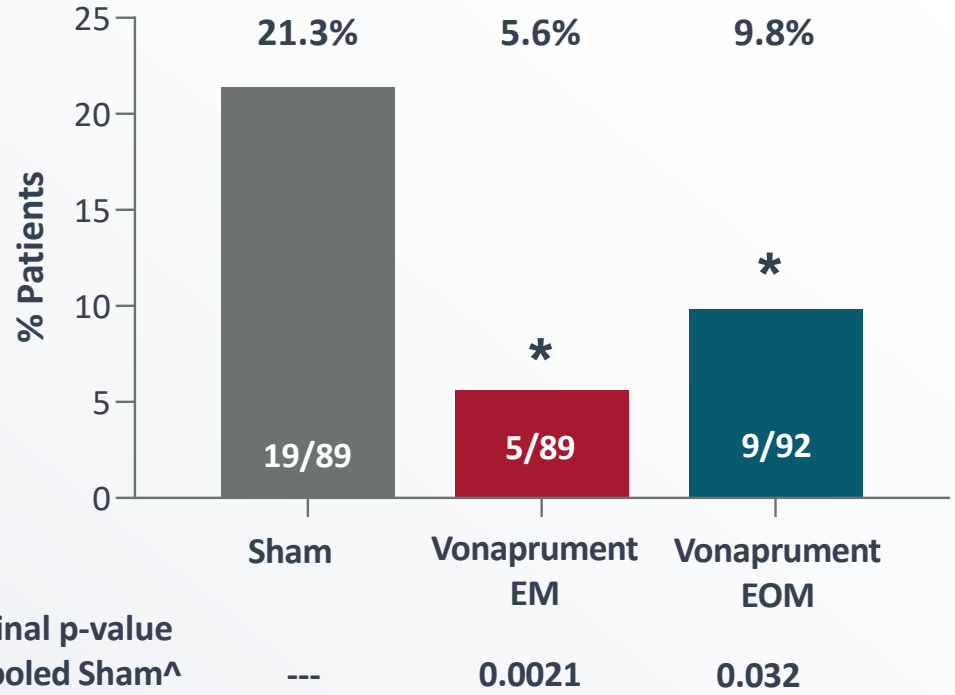
##Confirmed for two consecutive visits through month 12; month 12 confirmed at month 15 visit

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

* P < 0.05

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#

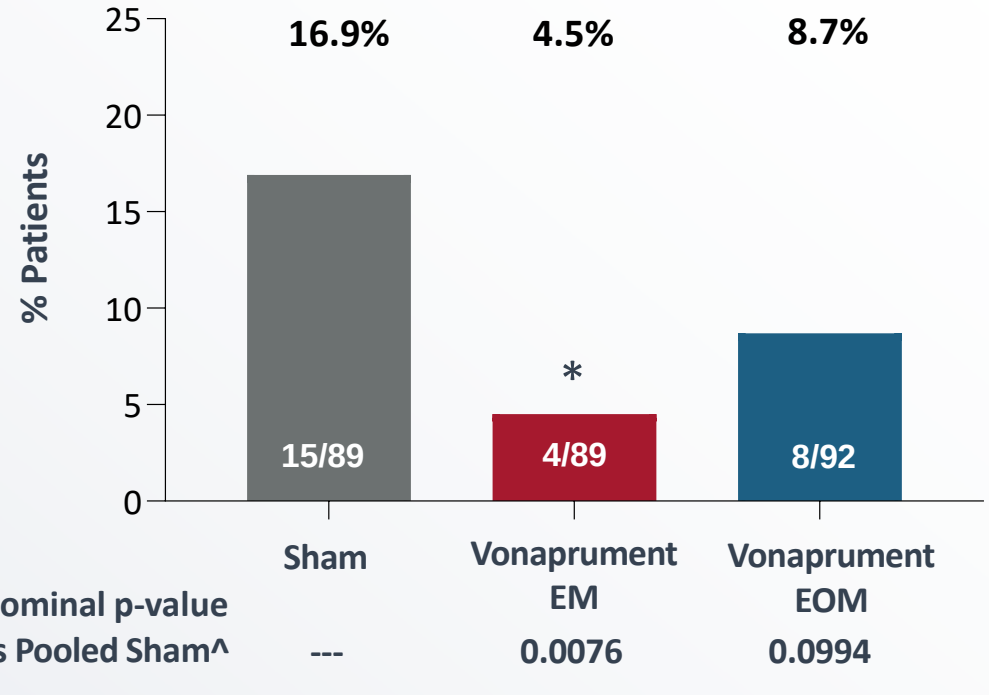


Nominal p-value vs Pooled Sham^	---	0.0021	0.032

#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

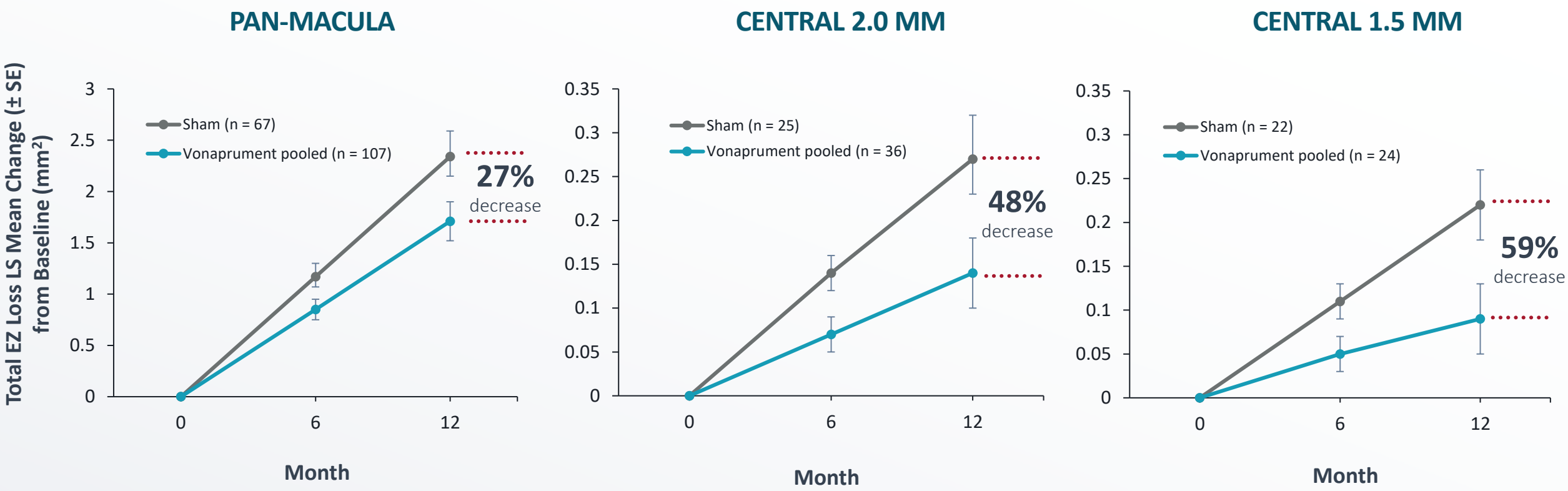


Nominal p-value vs Pooled Sham^	---	0.0076	0.0994

##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

Numerically Greater Photoreceptor Protection in Central Macula with Vonaprument

Comparison of Vonaprument effect on Ellipsoid Zone (EZ) across macula and in central subdomains 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

ARCHER: Key Safety Data

ADVERSE EVENTS OF SPECIAL INTEREST n (%)	SHAM (N=89)	VONAPRUMENT EM (N=89)	VONAPRUMENT 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	0	0	0
Intraocular Inflammation+	0	2 (2.2%)	1 (1.1%)
Ischemic Optic Neuropathy+	0	0	0

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

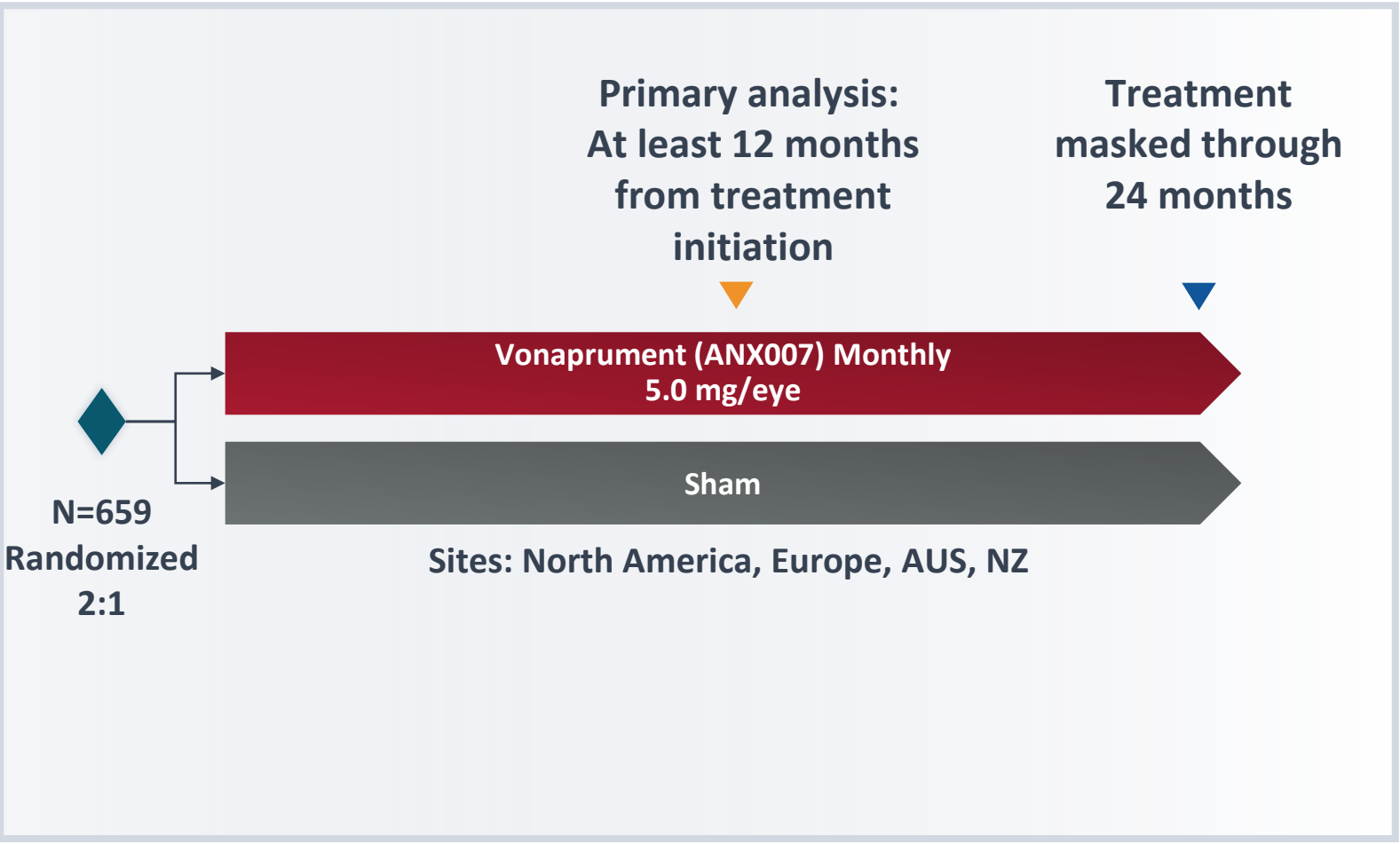
*Event Verbatim term listed

^Isolated cilioretinal artery occlusion; no vasculitis confirmed by DSMC and reading center
+Not AESI, included because of current interest

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

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

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

SECONDARY ENDPOINTS

Safety, LLVA, EZ integrity

Conclusions: C1q Inhibition

- **C1q Inhibition across several neurodegenerative diseases appears to convey protective effects resulting in functional benefits**
  - ANX005 improved measures of clinical function in HD patients with high baseline levels of complement activity in a Phase 2 trial
    - Outcomes in the phase 2 ARCHER trial in eyes with dry AMD/GA suggest vonaprument may provide protection against the risk of vision loss and the loss of synapses and photoreceptors
- **Clinical trials are ongoing in multiple serious autoimmune & neurodegenerative diseases**
- **Phase 3 ARCHER II trial of vonaprument in Dry AMD with GA:**
  - **Is the only global pivotal program with vision preservation as the primary endpoint**
  - **Has a path to global registration**
    - **EMA: PRIME designation; Selected to Participate in Product Development Coordinator Pilot**
    - **FDA: Fast Track Designation**
  - **Has completed enrollment; Data Expected 2H 2026**