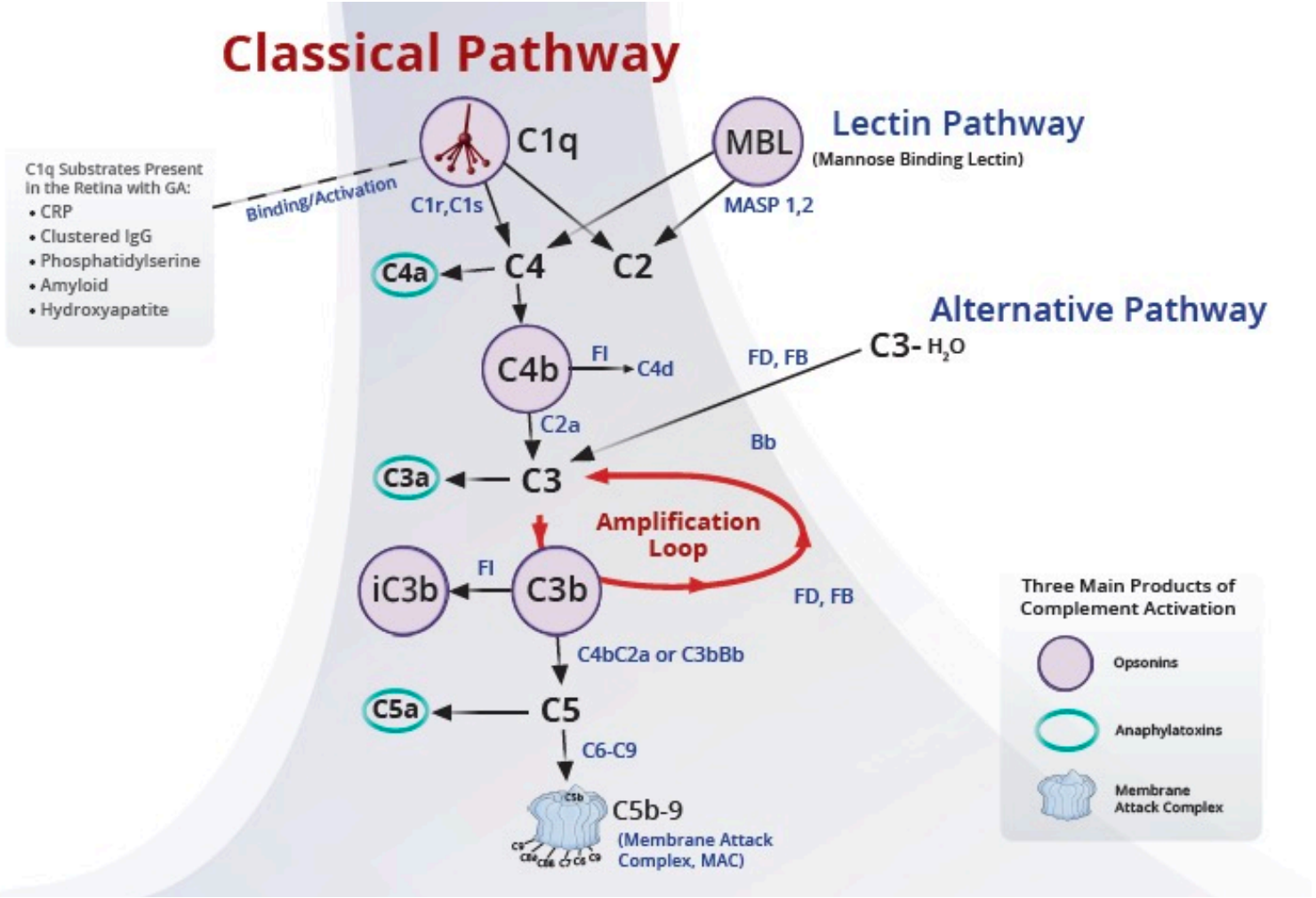
Role of C1q Inhibition in the Treatment of Geographic Atrophy Secondary to Age-related Macular Degeneration

David Boyer, MD

C1q and Classical Complement Pathway

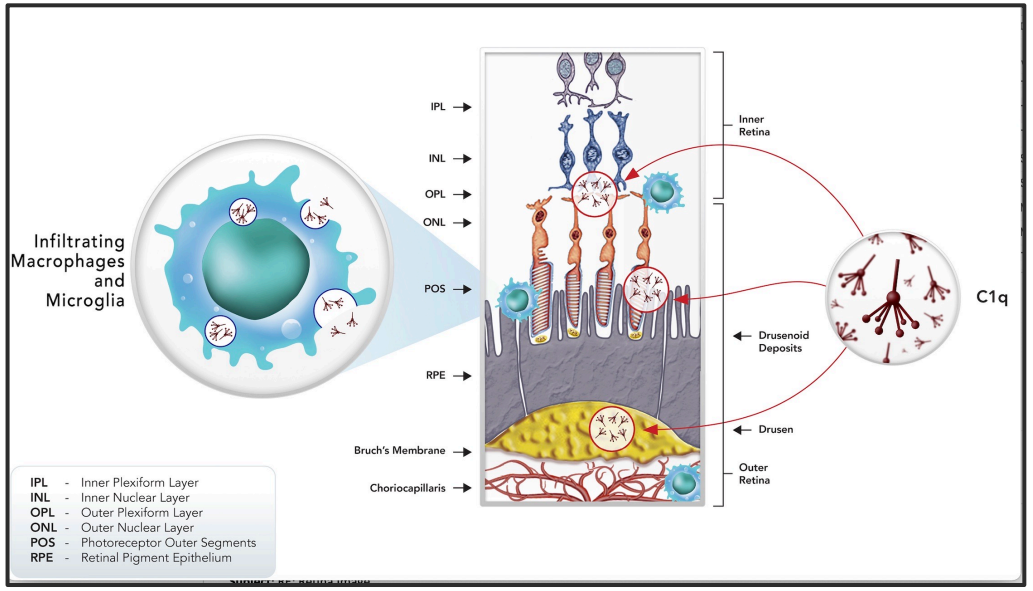


Selective inhibition of C1q shuts down all tissue-damaging components of classical pathway (C4, C3, C5, C9) while allowing immune functions of lectin and alternative complement pathways to continue without disruption

Katsche et al. Scientific Reports 2018
Law and Dodds. Protein Science 1997
Chirco and Potemp. Front Immunology 2018

C1q and Classical Cascade are Key Drivers in Geographic Atrophy

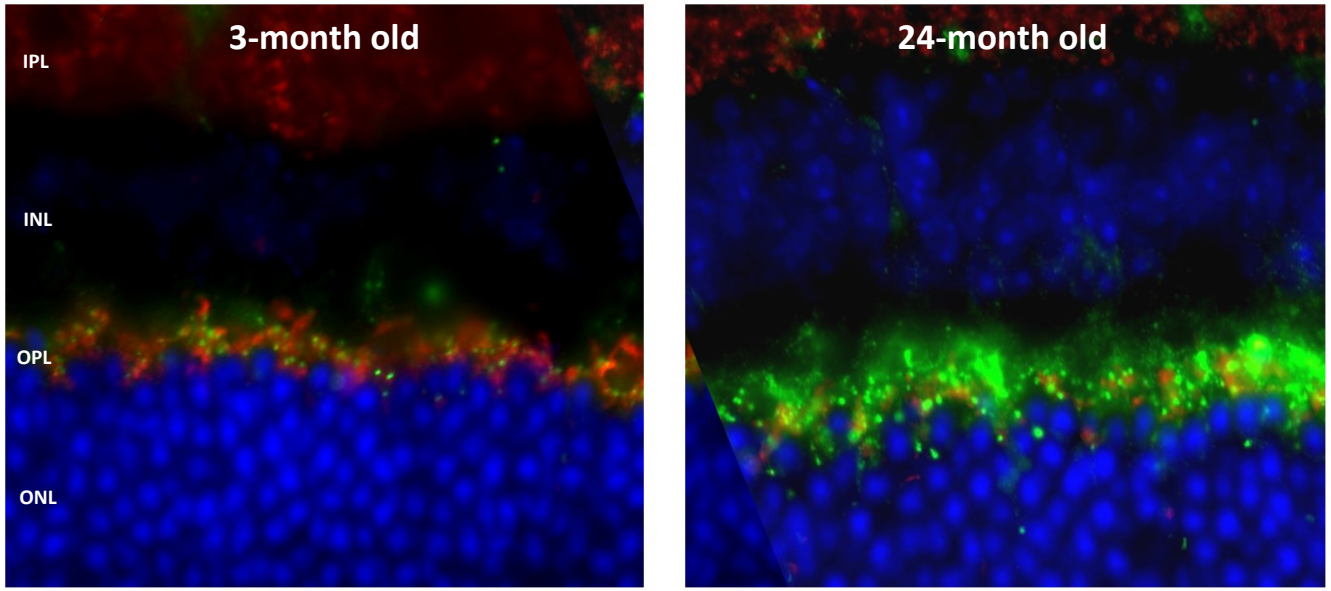
- **High local expression of C1q in the retina by infiltrating macrophages**
  - Macrophages in OPL, POS, RPE, choroid express high levels of C1q
- **C1q activators present in all layers of the outer retina**
- **C1q and downstream activated complement components are deposited in multiple layers of outer retina in GA**
- **Blocking C1q / classical pathway protects photoreceptor cells and function in photoreceptor damage models**



Fletcher , Ophthalmic Physiologic Optics 2020
Jiao et al, Molecular Neurodegeneration 2018

C1q Accumulates with Age in Geographic Atrophy

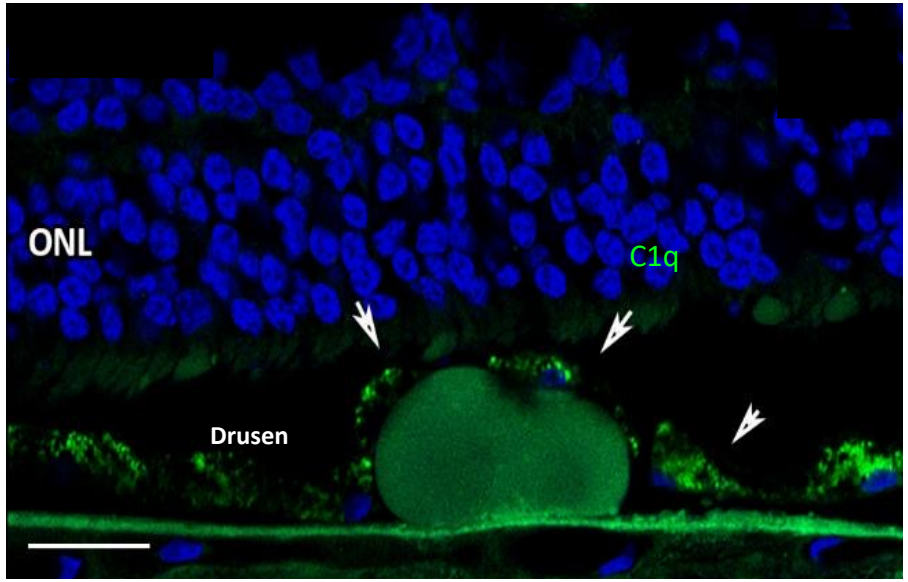
C1q accumulation on photoreceptor cell synapses in mouse retina



Synapses C1q Nuclei

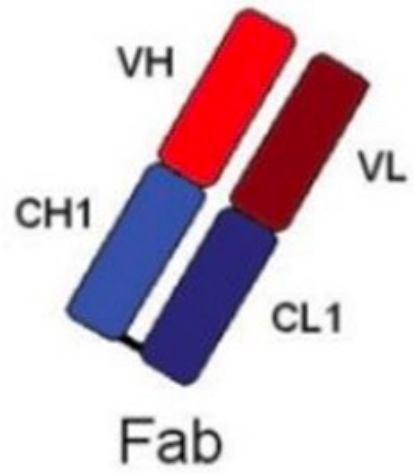
Data on File, Annexon Biosciences

C1q accumulation on drusen in human retina with GA



Human retinal micrograph: Jiao, et al., Mol Neurodegener. 2018 08 20;13(1):45

ANX007 is Designed to Inhibit C1q

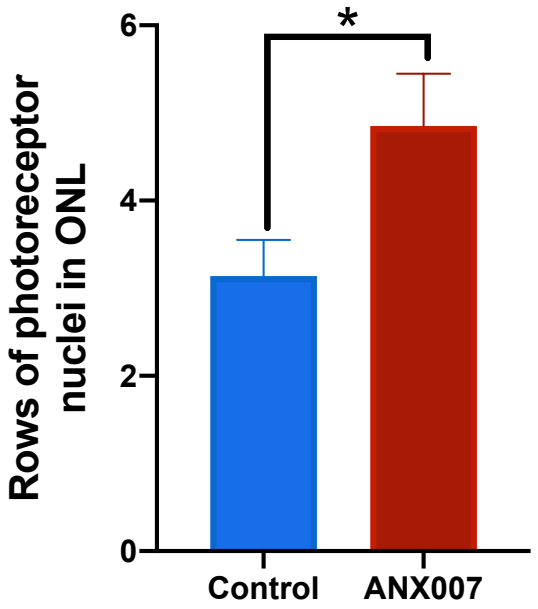


- Recombinant humanized antigen binding fragment (Fab) of a monoclonal antibody
- Composed of one VH and CH1 segment of an IgG1 heavy chain covalently linked to one kappa light chain
- Molecular weight - ~48 kDa
- Binds to the complement protein C1q via its antigen binding domain

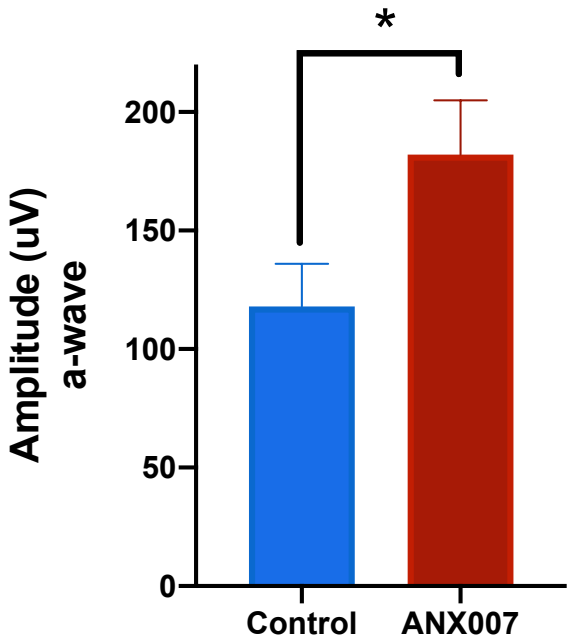
ANX007 Provides Neuroprotection in a Mouse Model

Intravitreal Administration of ANX007 Protects Photoreceptor Cells and Retinal Function

Anti-C1q Protects Photoreceptor Cells / Retinal Thickness



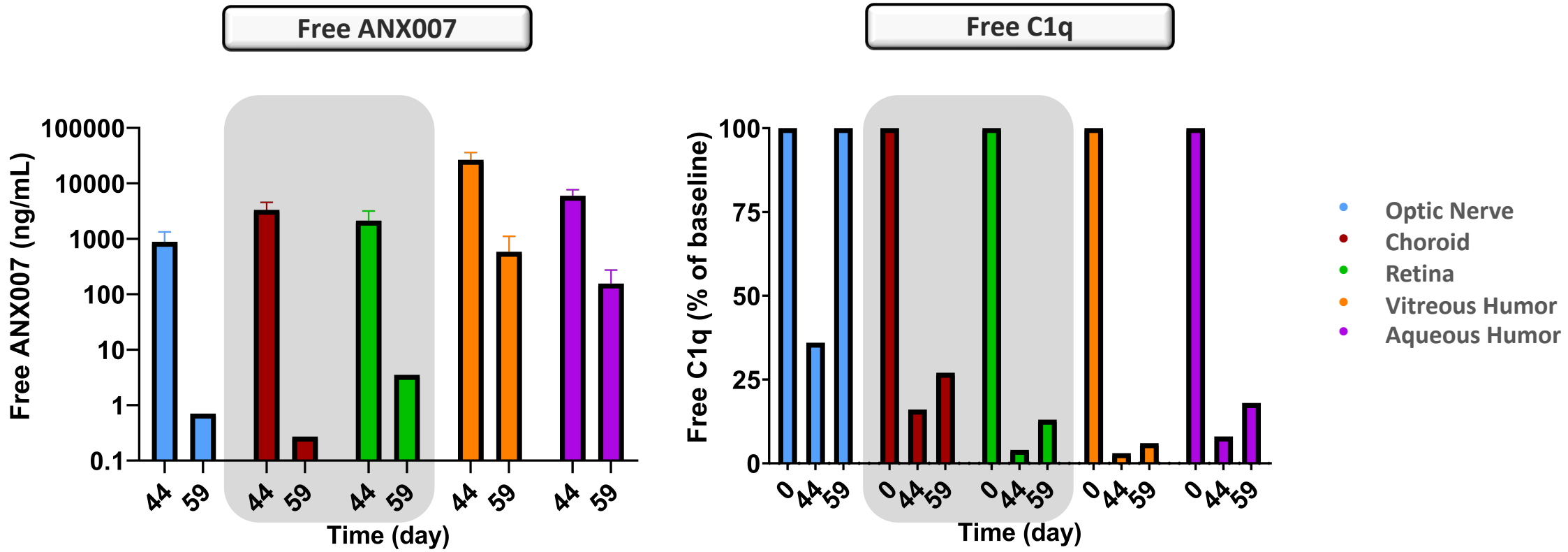
Protects Retinal Function



** p < 0.05;*

Jiao et al., 2018 Mol Neurodegener 13(1):45

ANX007 Reduces C1q Levels in Retina of Non-Human Primates

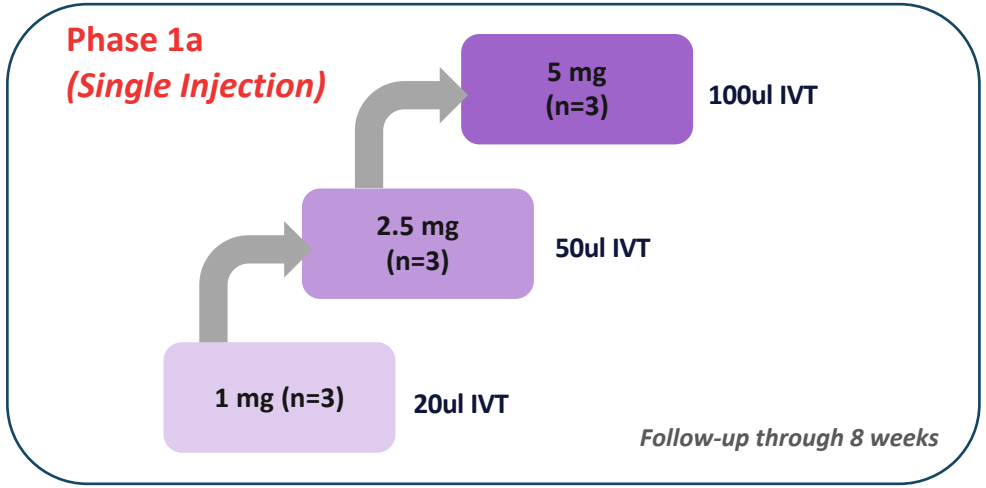


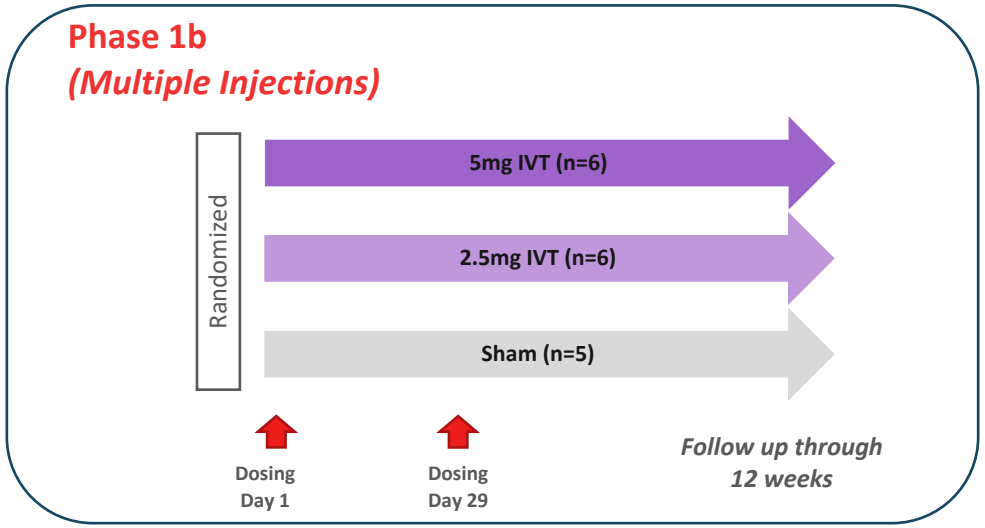
Two doses of 5 mg ANX007 administered IVT 28 days apart in cynomolgus monkeys

- ***Day 44*** *= 15 days post-last dose*
- ***Day 59*** *= 30 days post-last dose*

Grover A, et al. IOVS 2021;62:ARVO E-Abstract 219

Phase 1 Studies in Glaucoma



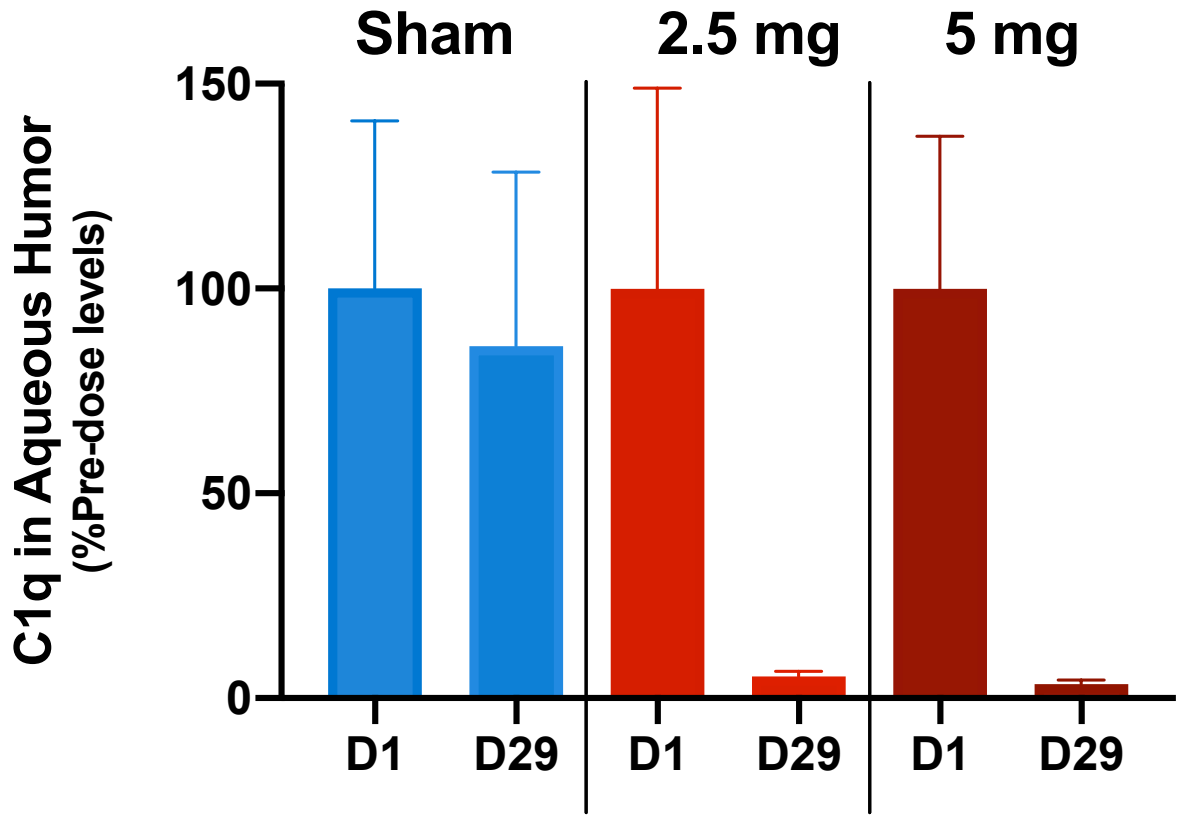


SUMMARY

- Repeat doses, in patients with Primary Open-Angle Glaucoma *(n=17)*
- Well-tolerated at all dose levels
  - No SAEs or severe TEAEs
  - All AEs were mild in severity and resolved
  - Ocular TEAEs (ocular irritation, subconjunctival hemorrhage or conjunctival hyperemia) consistent with other IVT administered treatments

Data on File, Annexon Biosciences

ANX007 Effectively Inhibits C1q



D1 *= Day 1 (before ANX007 dosing)*

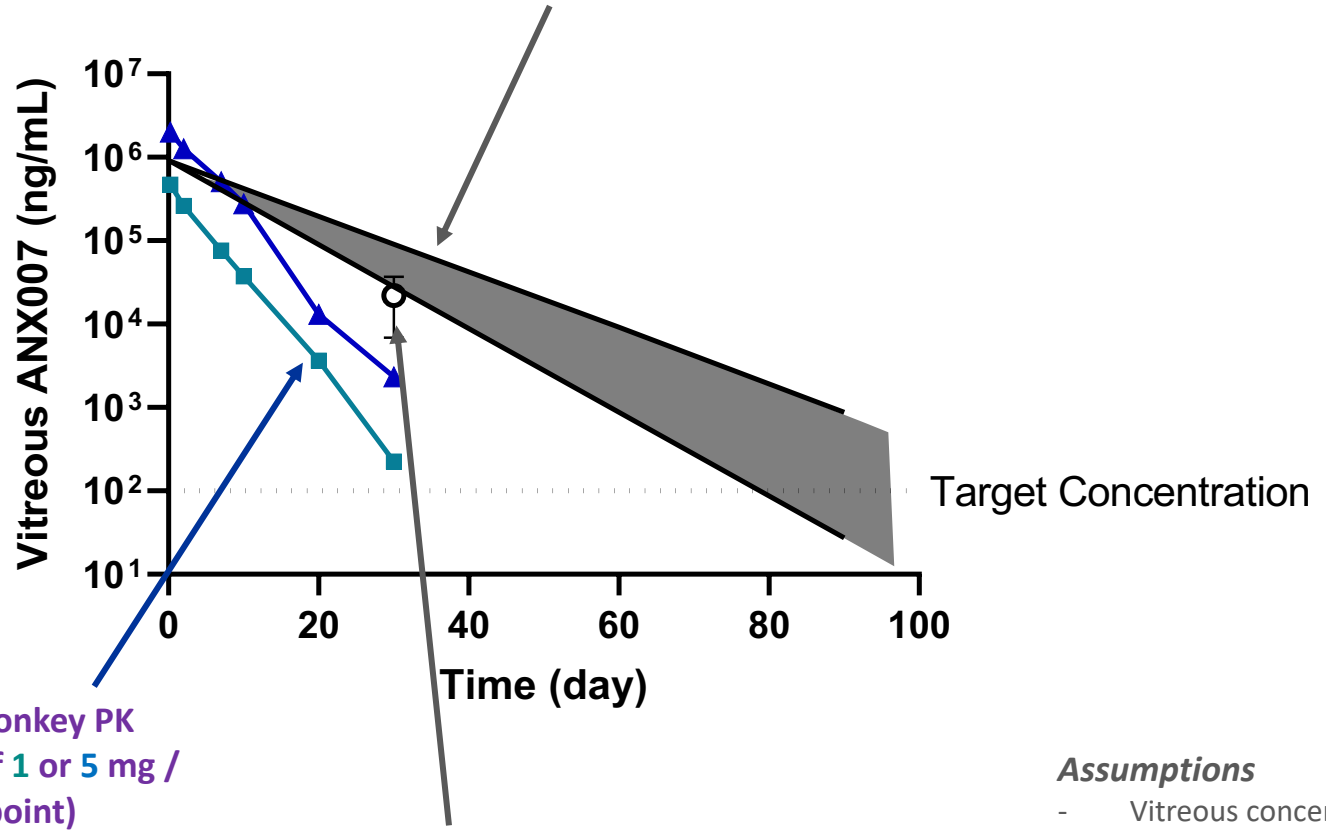
D29 *= Day 29 (post-1st dose)*

Single intravitreal injection ***inhibited C1q in aqueous humor for at least 29 days*** at both doses

Data on File, Annexon Biosciences

C1q Inhibition in Vitreous Projected to be Maintained for at Least 2 Months

Projected ANX007 PK in human vitreous following a 5 mg dose based on observed data from cynomolgus monkey



Observed cynomolgus monkey PK following a single dose of 1 or 5 mg / eye (mean of n=2 / timepoint)

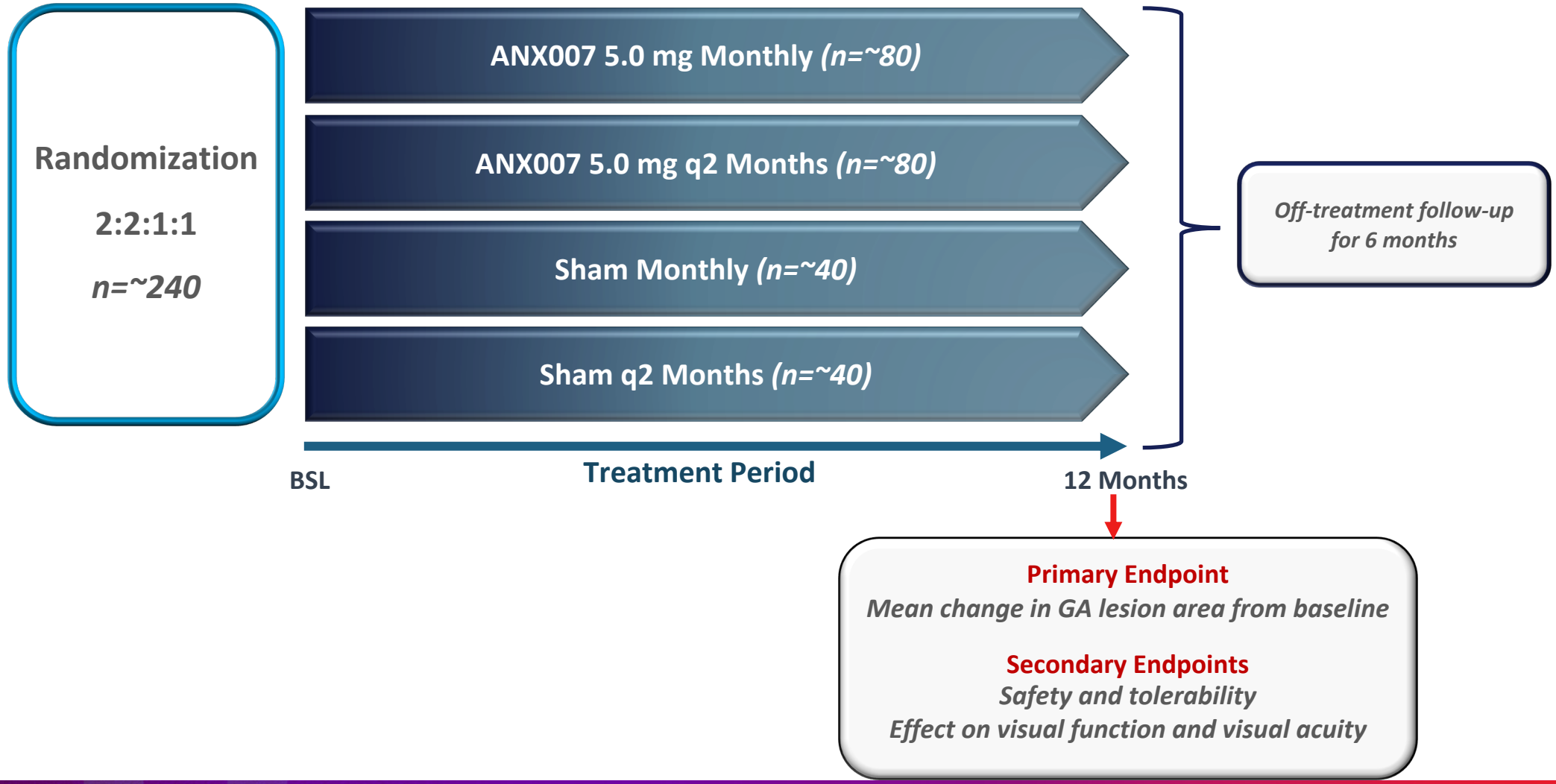
Calculated vitreous concentration, based on observed aqueous PK in ANX007 phase 1b glaucoma study (n=3, mean ± SE)

Assumptions

- Vitreous concentrations are 4x aqueous concentrations based on observed cynomolgus monkey data
- Human ocular half life is 3x cynomolgus monkey ocular half life based on published data from other IVT-administered Fabs (*Xu et al, IOVS 2013 54(3):1616-24)*

Data on File, Annexon Biosciences

The ARCHER Study: *Ongoing Phase 2 Study Evaluating Effect of ANX007*



Summary

- C1q, the initiating molecule of the classical complement cascade, has been implicated in neurodegenerative diseases, including GA
- ANX007 is designed to inhibit C1q while allowing immune functions of lectin and alternative complement pathways to continue
- IVT ANX007 was well- tolerated in Phase 1 studies in glaucoma
- Ongoing ARCHER study evaluates GA lesion growth rate following IVT ANX007 (5 mg q1 month or q2 months) compared to sham
  - Lesion sizes inclusive of > 2.5 mm^2 – 17.5 mm^2 *(~1-7 DA or if multifocal, one lesion ≥ ½ DA)*
  - CNV in fellow eye allowed

  FPI: Q1'21; results anticipated in 2023