Safety, tolerability and target engagement of intravitreal (IVT) ANX007 injections in primary open-angle glaucoma (POAG)

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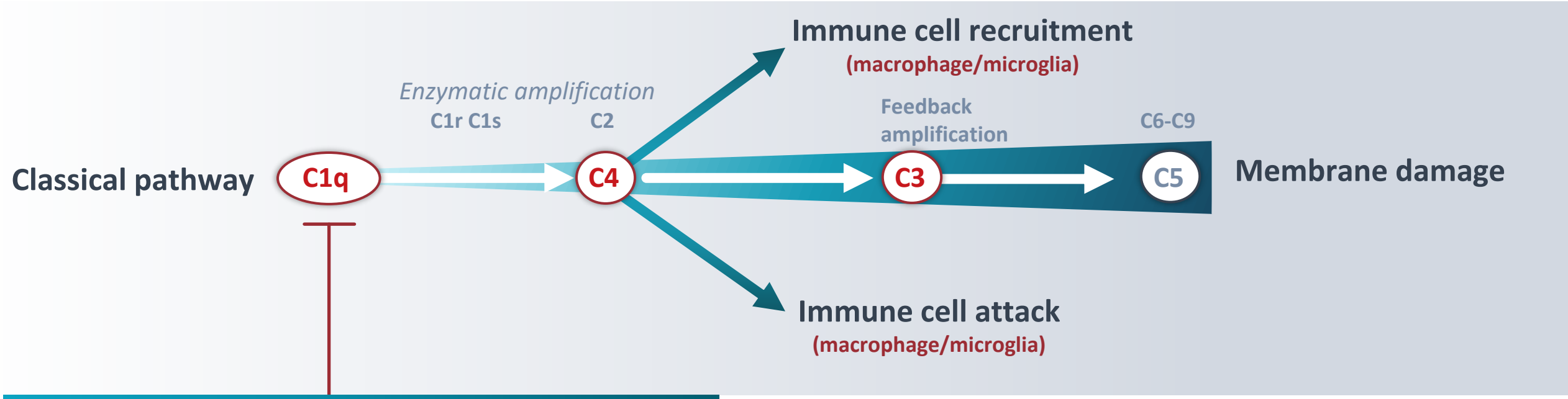
American Academy of Ophthalmology
November 13-15, 2020

Author Disclosures

- **Yang Sun:** Has no potential conflicts of interest to disclose.
- **David Wirta:** Received grant support from Annexon Biosciences.
- **Vidhu Mathur, Sethu Sankaranarayanan, Ted Yednock, Sanjay Keswani:** Full-time employees of Annexon, and may hold Annexon stock and/or stock options.
- **Jeffrey L Goldberg:** Consultant to Annexon Biosciences.

The authors wish to acknowledge **Kuldev Singh, MD, Robert Chang, MD,** and **Caroline Fisher, MD, Steve Sanislo, MD,** and **Ted Leng, MD,** for their participation and **Zhongqiu Li, Supriya Kawale, Gala Beykin, MD,** and **Mariana Nunez** for their assistance with clinical research coordination.

ANX007, an Anti-C1q Antibody Fragment, Blocks Classical Complement Pathway Activation[1-3]



ANX007 and related molecules

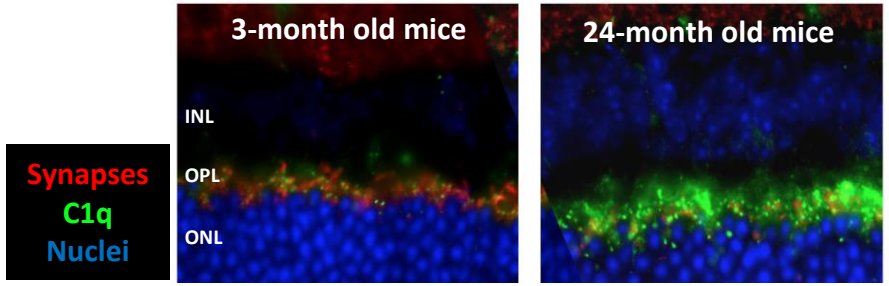
Inhibiting C1q upstream blocks downstream inflammatory activities of the complement pathway

References: 1. Carpanini SM, et al. *Front Immunol.* 2019;10:362. 2. Dunkelberger JR, Song WC. *Cell Res.* 2010;20(1):34-50. 3. Data on file. Annexon, South San Francisco, CA.

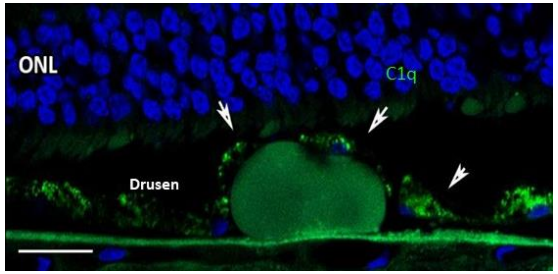
Classical Pathway and C1q Associated With Neurodegenerative Diseases of the Eye

C1q accumulation on both sides of photoreceptors – key neurons lost in geographic atrophy (GA)

C1q accumulation on photoreceptor cell synapses in mouse retina with age[1]

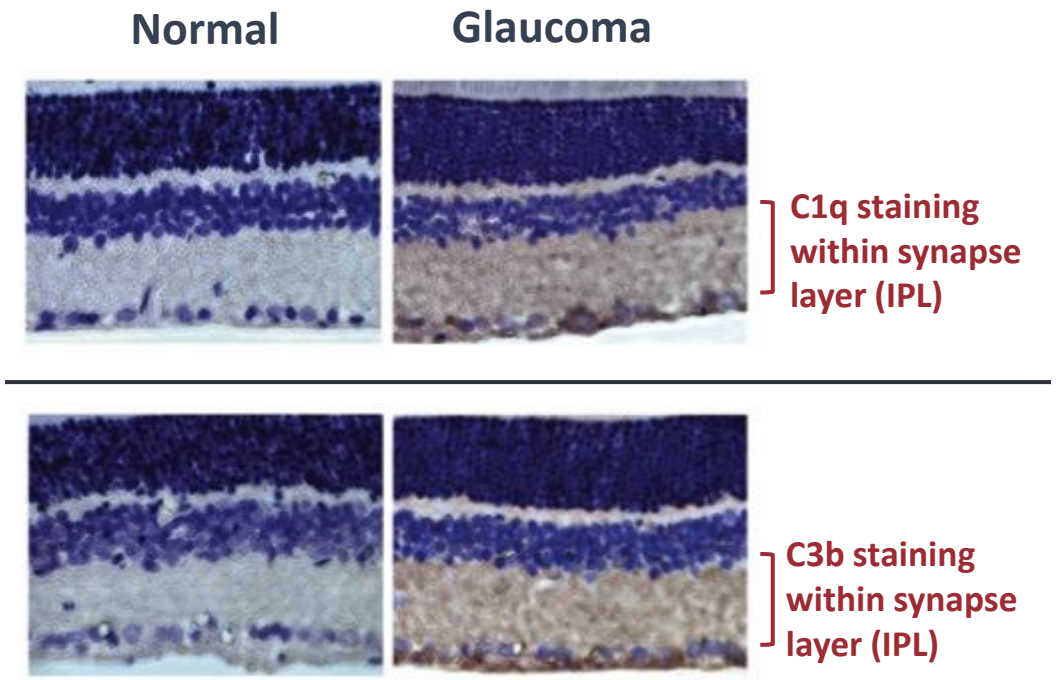


C1q also accumulates on drusen on the other side of the photoreceptors in humans[2]



Adapted from Jiao H, et al. *Mol Neurodegener.* 2018;13(1):45 with permission from the Creative Commons Attribution 4.0 International License. https://creativecommons.org/licenses/by/4.0/.

Synapses of retinal ganglion neurons are tagged by C1q and C3b in tissue from glaucomatous eyes[3]



Adapted from Tezel G, et al. Oxidative stress and the regulation of complement activation in human glaucoma. *Invest Ophthalmol Vis Sci.* 2010;51(10):5071-5082. with permission from the Association for Research in Vision and Ophthalmology.

Elevated C1q and C3b was seen in 34/34 glaucoma patients

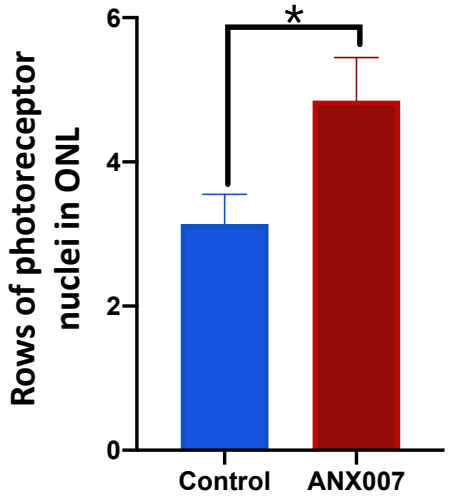
GA, geographic atrophy; INL, inner nuclear layer; IPL, inner plexiform layer; ONL, outer nuclear layer; OPL, outer plexiform layer.

References: 1. Data on file. Annexon, South San Francisco, CA. 2. Jiao H, et al. *Mol Neurodegener.* 2018;13(1):45. 3. Tezel G, et al. *Invest Ophthalmol Vis Sci.* 2010;51(10):5071-5082.

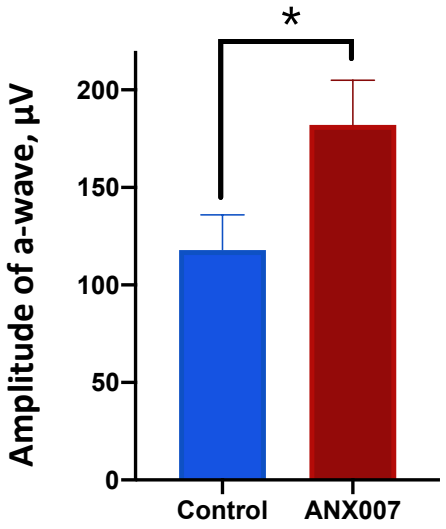
Intravitreal Administration of Anti-C1q Provides Neuroprotection in Ophthalmic Diseases

Protective of photoreceptor cells and retinal function in model of GA-like damage[1]

Anti-C1q protects photoreceptor cells/retinal thickness

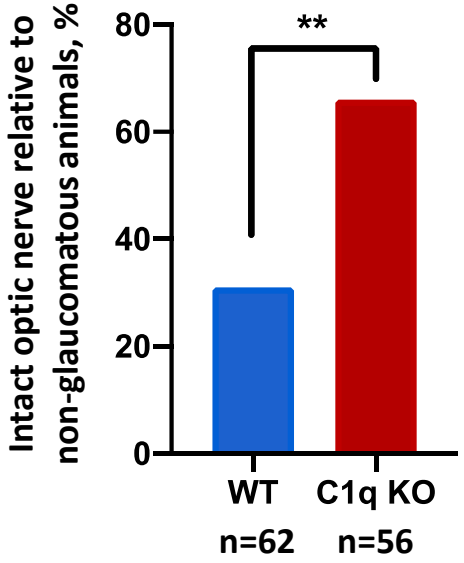


Protects retinal function

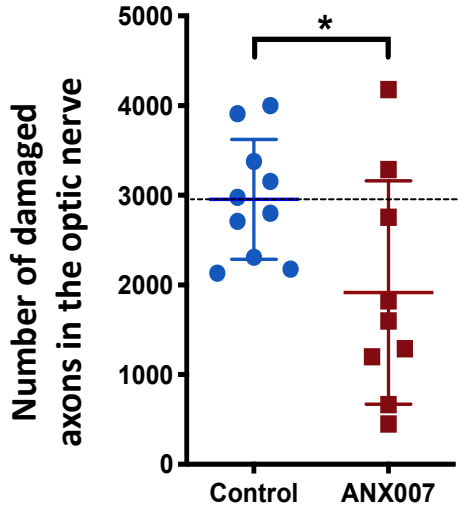


Protective in both acute and chronic models of glaucoma

C1q KO protected optic nerve integrity at 12 months of age[2]



Anti-C1q protected against acute optic nerve damage[3]



Adapted from Howell GR, et al. *J Clin Invest.* 2011;121(4):1429-1444. with permission from the American Society for Clinical Investigation.

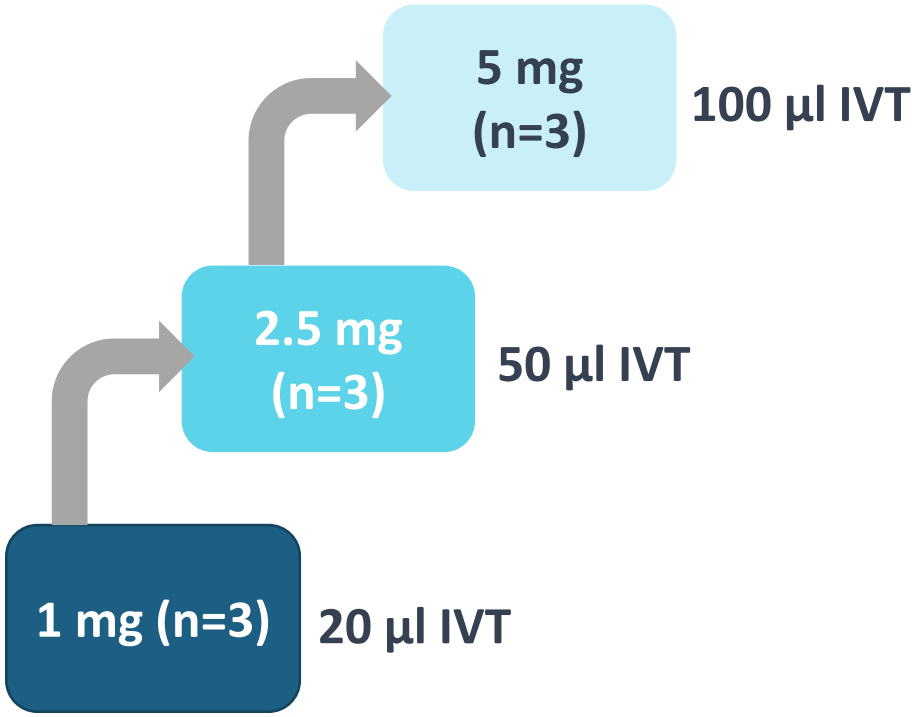
*P<0.05; **P<0.001

GA, geographic atrophy; KO, knockout; ONL, outer nuclear layer; WT, wild type.

References: 1. Jiao H, et al. *Mol Neurodegener.* 2018;13(1):45. 2. Howell GR, et al. *J Clin Invest.* 2011;121(4):1429-1444. 3. Data on file. Annexon, South San Francisco, CA.

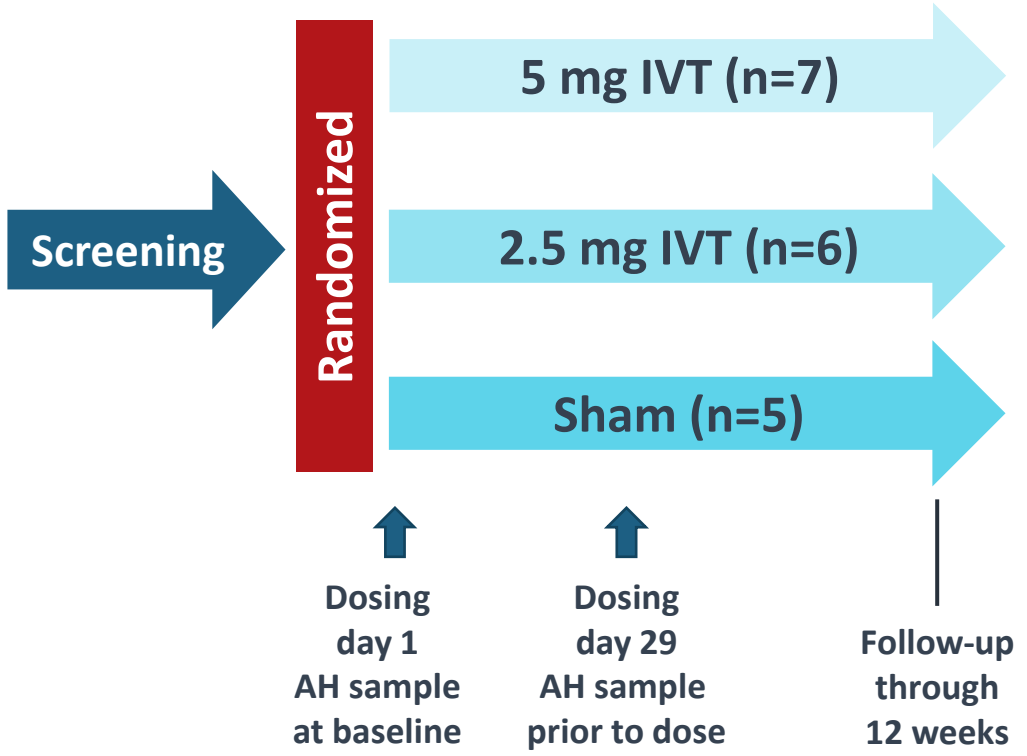
Phase 1 Studies Assessing the Safety and Tolerability of ANX007 in Those With Glaucoma

ANX007-GLA-01 phase 1a study



- Single ascending doses in participants with glaucoma
- Follow-up through 8 weeks

ANX007-GLA-02 phase 1b study



- Two monthly doses in participants with glaucoma
- AH samples were also collected to assess PK/PD

AH, aqueous humor; IVT, intravitreal; PD, pharmacodynamics; PK, pharmacokinetics.

Inclusion/Exclusion Criteria and Patient Disposition

INCLUSION/ EXCLUSION CRITERIA

- Adults with POAG with a mean deviation between –3 and –24 db
- IOP <21 mmHg at screening and day 1 with stable medications
- No cataract surgery <3 months prior to injection, or trabeculectomy, iridotomy, vitrectomy or other ocular procedures in the study eye that could affect drug distribution and excretion
- No treatment with an investigational therapeutic agent within 30 days (or 5 half-lives for small molecule agents) prior to injection, with the exception of IVT injection studies, in which case 90 days are required

ANX007-GLA-01 phase 1a study

- **Participants enrolled (n=9):** ANX007 1 mg, 2.5 mg, 5 mg
- **All participants completed the study**

ANX007-GLA-02 phase 1b study

- **Participants randomized (n=18):** sham, ANX007 2.5 mg, and ANX007 5 mg
- **Participants dosed (n=17):** 1 participant in the 2.5 mg group was not dosed due to elevated IOP on day 1
- **Participants completing the study (n=16):** 1 participant discontinued due to pseudoexfoliative glaucoma diagnosis

IOP, intraocular pressure; IVT, intravitreal; POAG, primary open-angle glaucoma.

IVT ANX007 Was Well-Tolerated in Phase 1 Studies

No SAEs, severe TEAEs, or fatal AEs

All AEs were mild in severity and resolved by the end of the study

- Ocular TEAEs were consistent with other IVT-administered treatments (ie, ocular irritation, subconjunctival hemorrhage, conjunctival hyperemia)

No ocular TEAEs in the non-study eye

No clinically significant laboratory results during study

After injection, IOP returned to normal by:

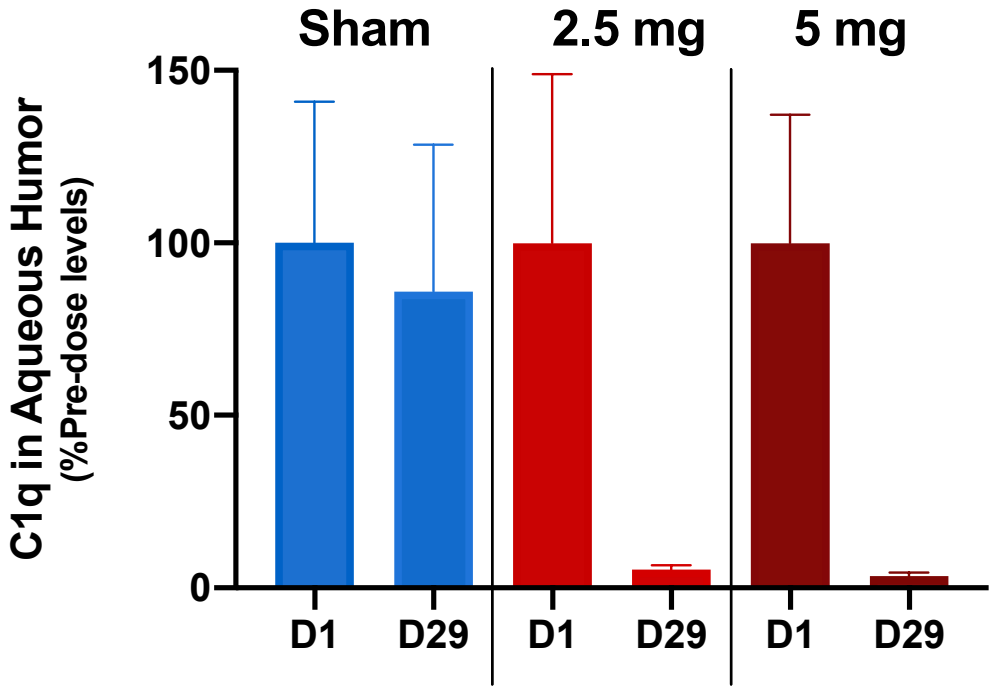
- 30 minutes in 25/26 participants
- 45 minutes in the remaining 1 participant

AE, adverse event; IOP, intraocular pressure; IVT, intravitreal; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Phase 1b: ANX007 Effectively Blocked C1q in Glaucoma Patients

- Single IVT injection **inhibited C1q for at least 29 days** in aqueous humor at both 2.5 mg and 5 mg doses
- Supports **monthly or less-frequent dosing** in ophthalmologic diseases

Free C1q levels in aqueous humor



D1 = Day 1 (before ANX007 dosing)

D29 = Day 29 (post-1st dose)

IVT, intravitreal.

Phase 1 Study of IVT ANX007 in Primary Open-Angle Glaucoma

TRIAL OBJECTIVES

- **Phase 1a single-ascending-dose study (N=9)**
- **Phase 1b repeat-dose study (N=17)**
- **Safety, tolerability, and PK/PD**
- **C1q target engagement**

ANX007 TOP-LINE SUMMARY

- **C1q, the initiating molecule of the classical complement pathway,** is a driver of neurodegenerative disease in the retina
- **Single and repeat IVT ANX007 injections were safe and well tolerated** in glaucoma patients
- **Full target engagement was seen 4 weeks** after dosing, supporting monthly dosing
- **Phase 2 studies are planned to assess efficacy and safety of IVT ANX007** in patients with GA

 GA, geographic atrophy; IVT, intravitreal; PD, pharmacodynamics; PK, pharmacokinetics.