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

Eleonora Lad, MD, PhD on behalf of the ARCHER study investigators

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

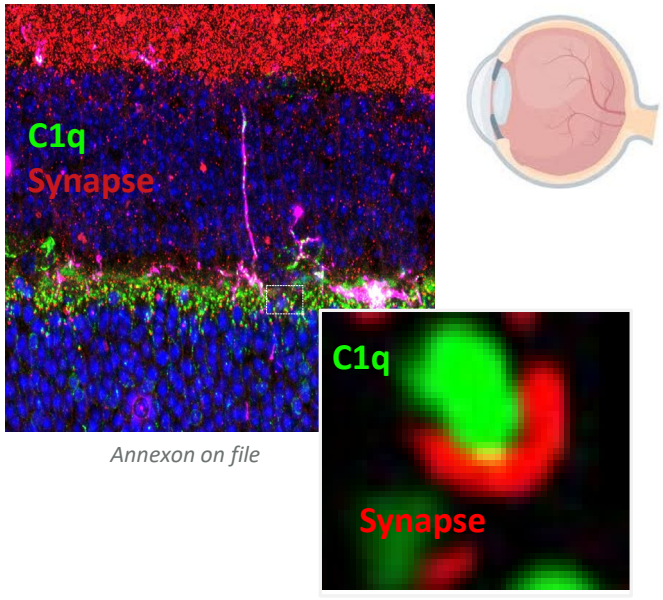
[1]Stevens, et al., 2007 DOI 10.1016/j.cell.2007.10.036; Schafer et al., 2012 DOI 10.1016/j.neuron.2012.03.026; Hong, et al., 2016 doi: 10.1126/science.aad8373; Lui et al., 2016 doi.org/10.1016/j.cell.2016.04.001; [2]Yednock, et al, 2022, doi.org/10.1186/s40942-022-00431-y

C1q is 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]

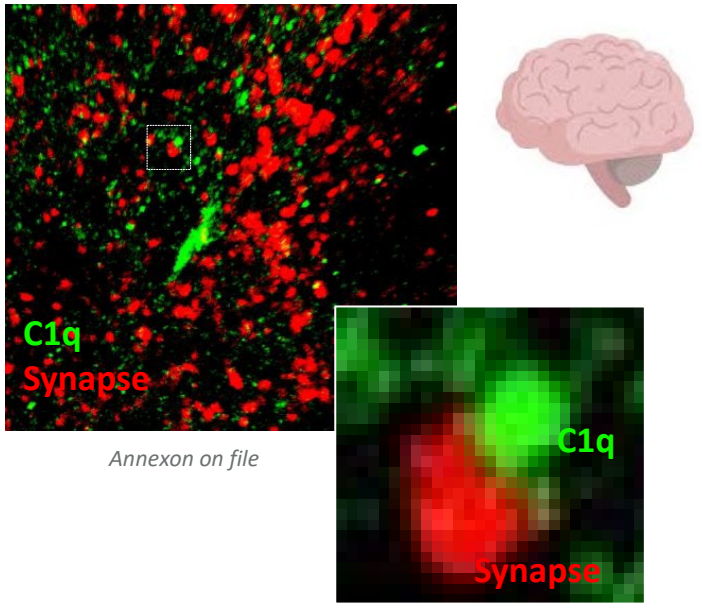
MODEL OF PHOTORECEPTOR DEGENERATION



Annexon on file

C1q targeting synapses for elimination in the brain[2]

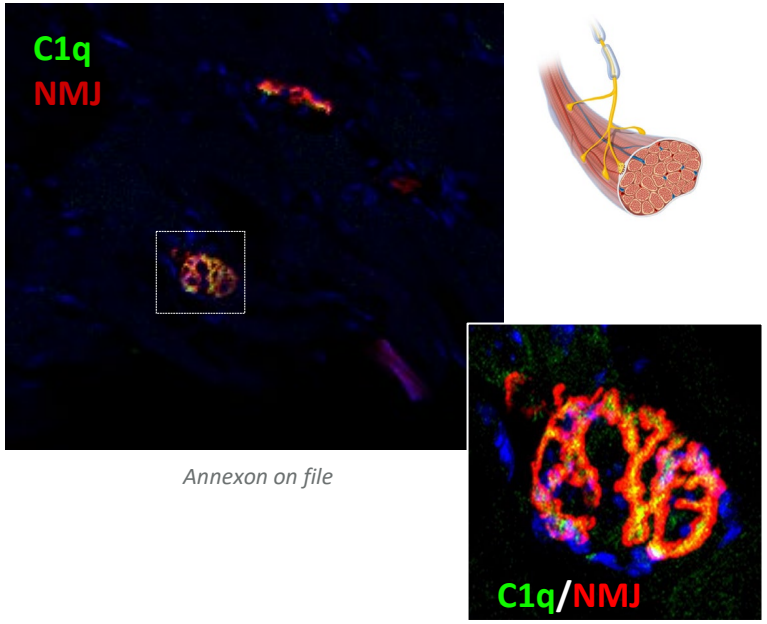
MODEL OF HUNTINGTON'S DISEASE



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]

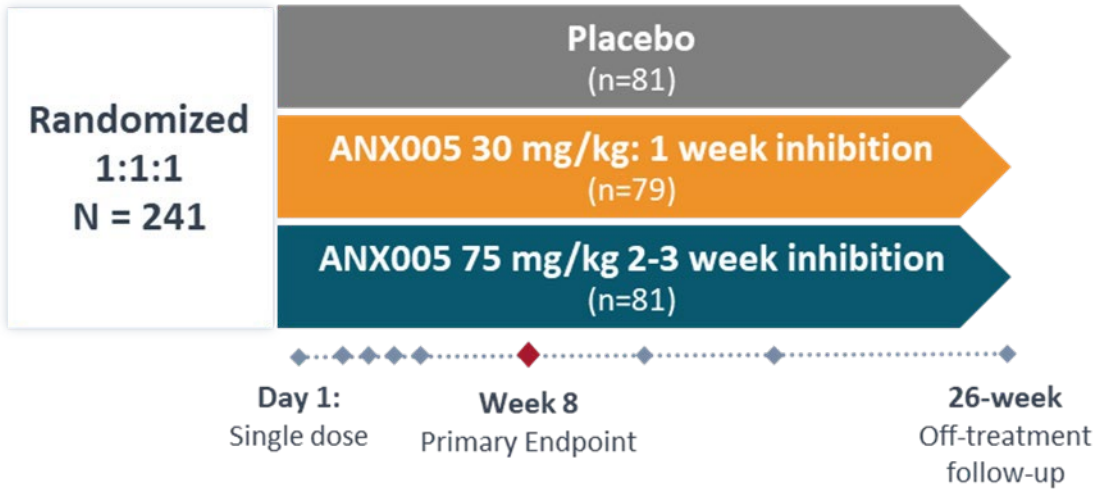
[1]Stevens, et al., 2007 DOI 10.1016/j.cell.2007.10.036; [2]Wilton, et al., 2023, doi: 10.1038/s41591-023-02566-3; [3]Idriss, et al., 2016 doi: 10.1186/s12974-016-0538-2
[4]Yednock, et al, 2022, doi.org/10.1186/s40942-022-00431-y

C1q Inhibition in Guillain-Barré Syndrome (GBS)

Phase 3 Pivotal Study Design

Randomized, Double-Blind, Placebo-Controlled Study

2 DOSES SELECTED TO DETERMINE MOST EFFECTIVE DURATION OF INHIBITION



ANX005 for GBS Granted FDA Fast Track and FDA / EMA Orphan Drug Designation

STUDY DESIGN

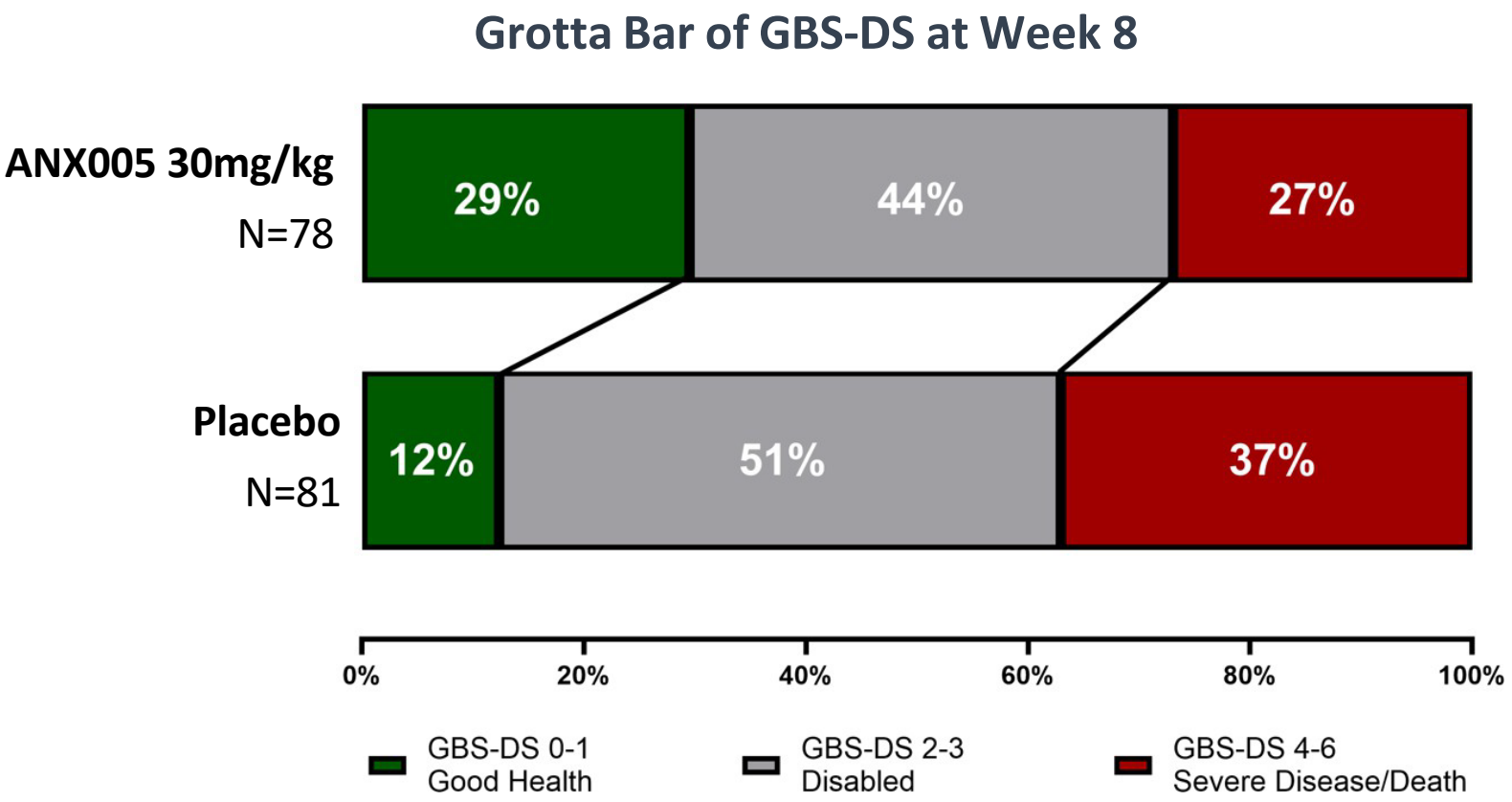
- Placebo-controlled (best standard of care, no IVIg or PE)
- Baseline GBS-DS score 3-5
- GBS diagnosed <10 days from onset of weakness
- Randomization stratified for baseline prognostic factors: muscle strength and time from onset of weakness
- Conducted in Bangladesh and Philippines given high prevalence of GBS of all types, scientific leadership in GBS, and limited access to IVIg

KEY ENDPOINTS

- **Primary Outcome Measure:** GBS-DS at week 8: well-accepted regulatory endpoint assessing functional status
- **Secondary Endpoints:** Muscle strength (MRC sumscore), Motor Disability (ONLS), Duration of Ventilation, and others

ANX005 30 mg/kg Showed Highly Significant Treatment Effect on GBS-DS* at Week 8 (Primary Endpoint)

2.41-fold higher likelihood of being in a better state of health relative to placebo



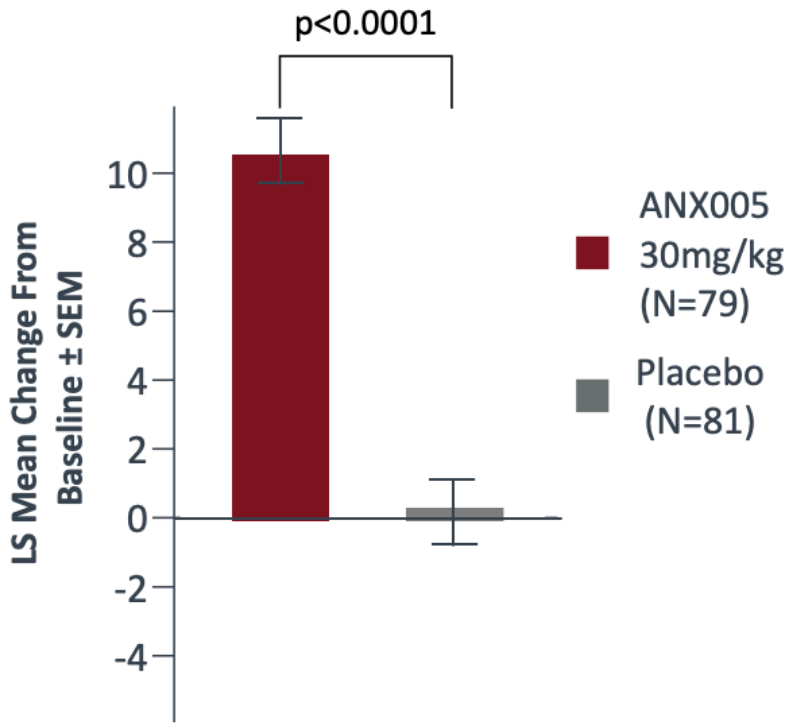
OR 2.41, p=0.0058

*GBS-DS, Guillain-Barré Syndrome Disability Scale

ANX005 Phase 3: Rapid Increase in Muscle Strength (Week 1) Translated to Long Term Benefit (Week 26) vs. Placebo

MORE THAN A 10-POINT IMPROVEMENT IN MUSCLE STRENGTH[1] OVER PLACEBO AT WEEK 1

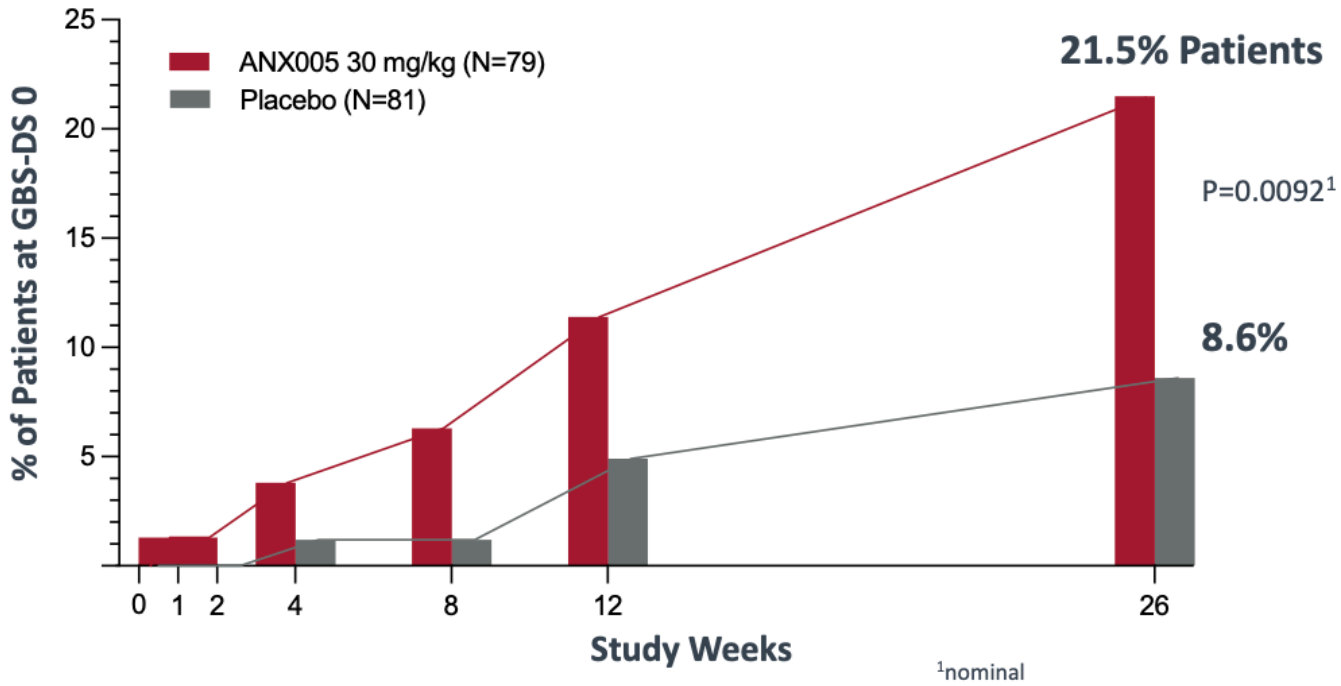
MRC Sumscore at Week 1



[1]Medical Research Council, MRC scale sumscore

2½ TIMES MORE TREATED PATIENTS FULLY RECOVER AT WEEK 26 (GBS-DS = 0)

GBS-DS Through Week 26



[1]nominal

Safety outcomes were similar to placebo

ANNEXON biosciences

C1q Inhibition in Huntington’s Disease (HD)

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

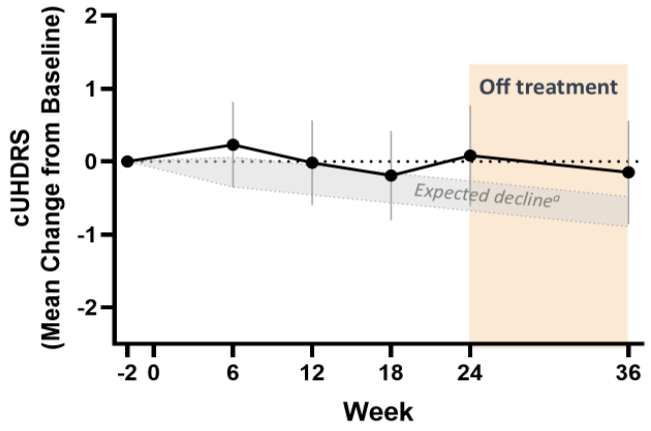
Study Design:

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

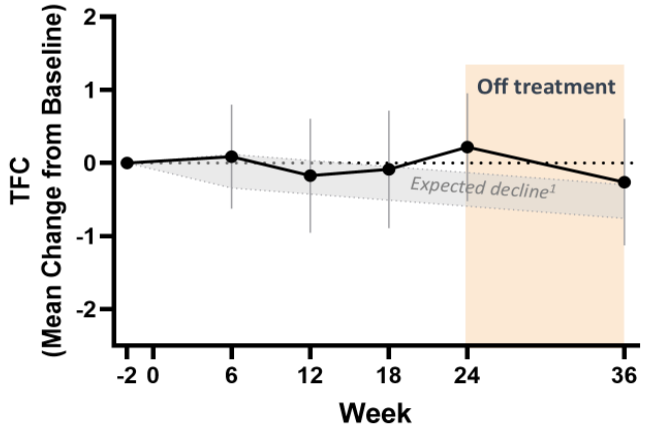
Follow up visits on Weeks 24, 28, and 36

Clinical Disease Progression Stable in ***Overall Patient Population*** Through On and Off-Treatment Periods (9 months)

cUHDRS Stable Over 9 Months (n=23)



TFC Stable Over 9 Months (n=23)



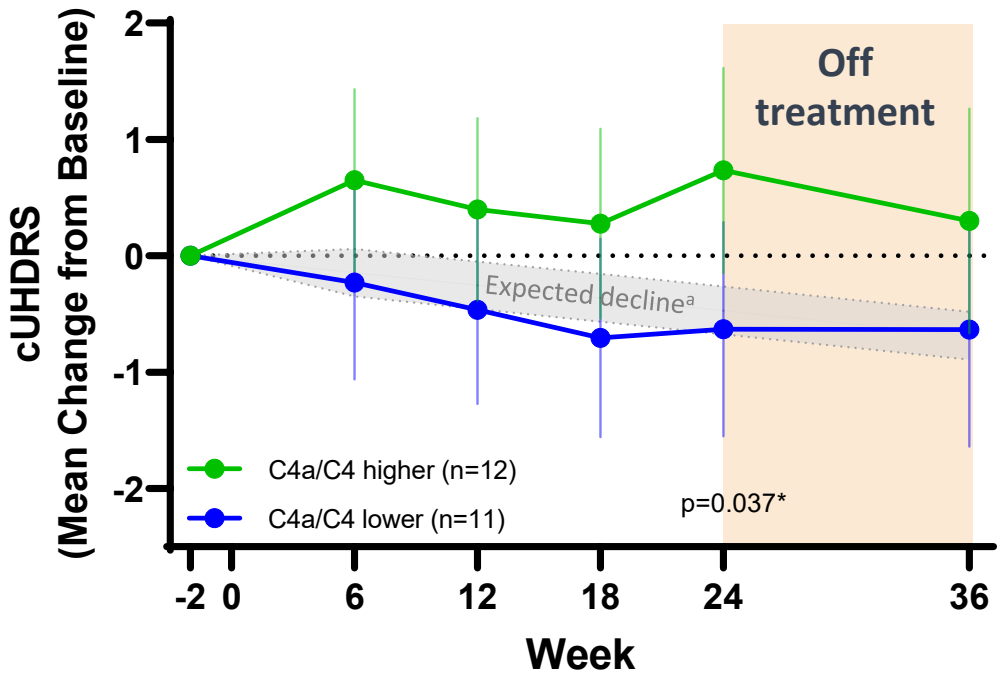
- UHDRS = Unified Huntington's Disease Rating Scale; a clinical rating scale to assess four domains of clinical performance and capacity in HD
- TFC = Total Functional Capacity; used to evaluate functional impairments across several domains in HD

MMRM; LS means +/- 95% CI

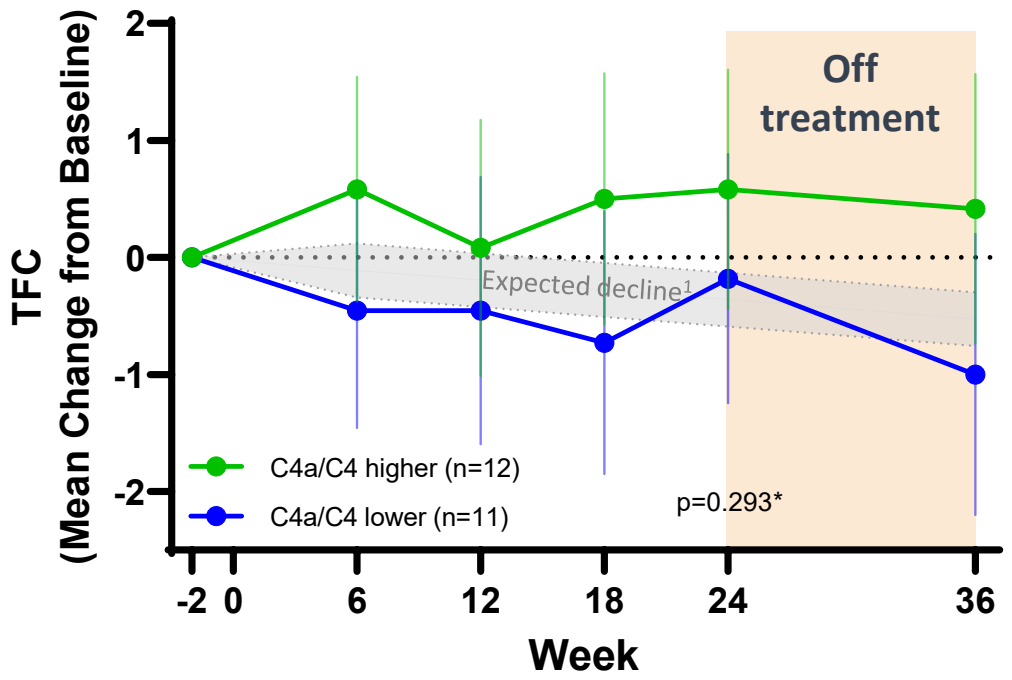
[a] Expected decline = interpolated natural history from Schobel 2017 (TRACK-HD)

Rapid Benefit Shown in Patients with ***Higher Baseline Complement Activity*** Through On- and Off-Treatment Periods (9 months)

Benefit at All Time Points in High Complement Group (cUHDRS)



Benefit at All Time Points in High Complement Group (TFC)



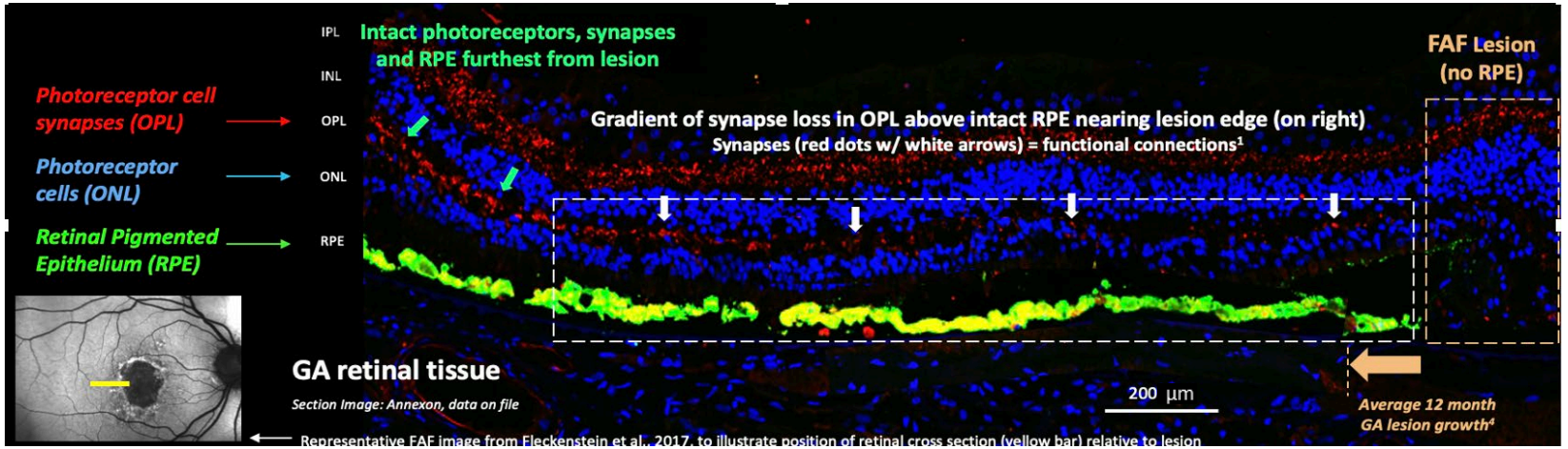
*Comparing higher vs lower C4a/C4 groups at week 2; MMRM; LS means +/- 95% CI; N=23.
[a]Expected decline = interpolated natural history from Schobel 2017 (TRACK-HD).
UHDRS = Unified Huntington's Disease Rating Scale; a clinical rating scale to assess four domains of clinical performance and capacity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

C1q Inhibition in Dry AMD and GA

Photoreceptor Cells and Synapses Loss Outside of GA Lesion

Human GA Retina

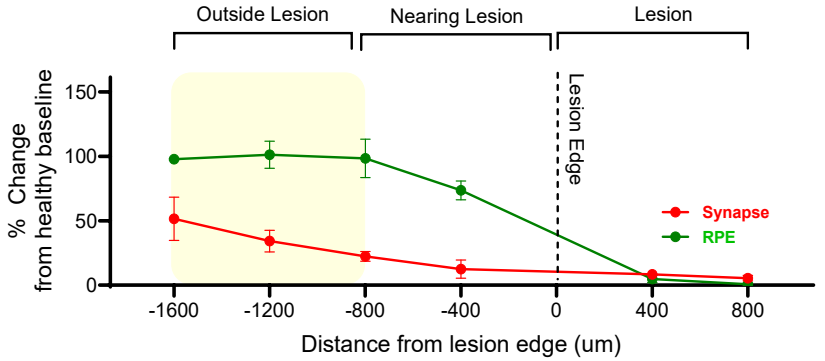
- Gradient of photoreceptor synapse and cell loss above intact RPE nearing lesion edge (white box)
- Photoreceptors are lost prior to RPE[1]; Loss of synapses is loss of function[2]
- FAF lesion growth tracks RPE loss, not photoreceptors, and correlates poorly w/ visual function[3]



Gradient of synapse loss above intact RPE nearing lesion edge

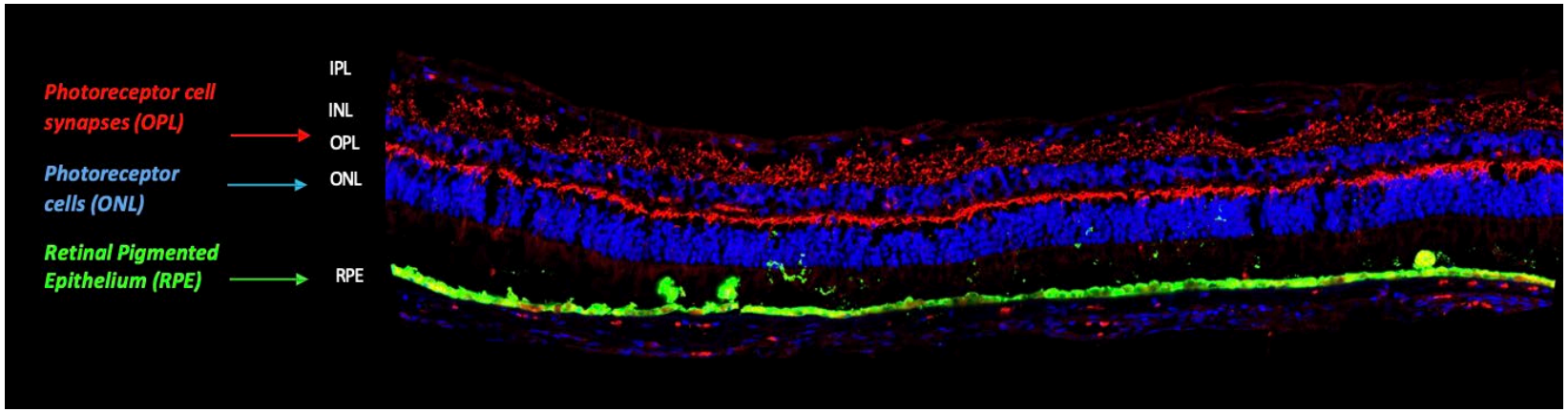
Photoreceptor Synapses
< 50% decrease outside lesion boundary

RPE cells integrity
intact in area of synaptic loss

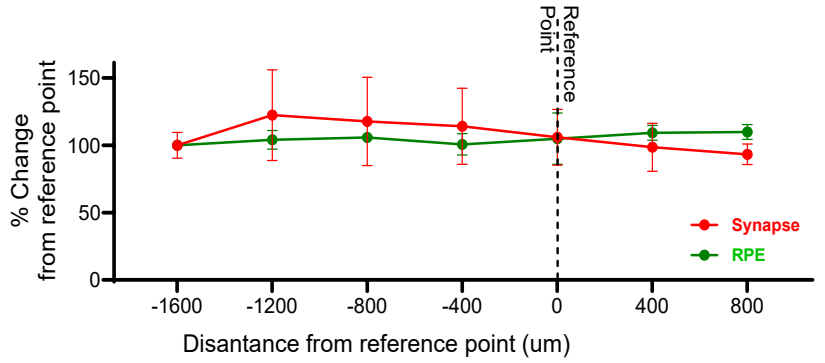


Healthy Human Retina

- Uniform layers of photoreceptor cells and synapses



Consistent synapse and RPE integrity across healthy retina



[1]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; [2]Selkoe, 2002 doi: 10.1126/science.1074069; Burger, et al., doi.org/10.1016/j.ydbio.2021.04.001; [3]Heier, et al., 2020 Ophthalmology Retina **4**:673; [4]Shen, et al., 2020 *Ophthalmol Retina* **4**:899

ARCHER: Phase 2 Trial – C1q Inhibitor ANX007 in Dry AMD and GA

ANX007: non-pegylated IVT-administered Fab – fragment of ANX005

Randomized, double-masked
Included **foveal and non-foveal** lesions
Stratified for lesion location and lesion size
12 months (n=270)

Sham monthly or every other month (n=89)	ANX007 5mg monthly (EM) (n=89)	ANX007 5mg every other month (EOM) (n=92)
PRIMARY BIOMARKER ENDPOINT	**EXPLORATORY BIOMARKER ENDPOINT**	**PRESPECIFIED FUNCTIONAL ANALYSES**
Change in GA lesion area as assessed by fundus autofluorescence at Month 12	Change in EZ lesion size at Month 12	Best Corrected Visual Acuity (BCVA) Low Luminance Visual Acuity (LLVA) & Deficit (LLVD)

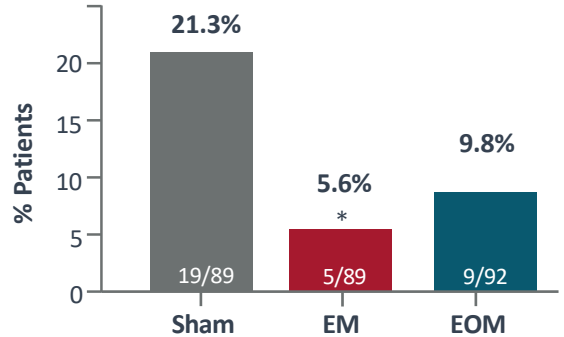
Off-treatment
(6 months)

END OF STUDY
Month 18

ARCHER: Phase 2 Study of patients with dry AMD & GA; ANX007 vs sham

REDUCED RISK OF BCVA ≥15-LETTER LOSS

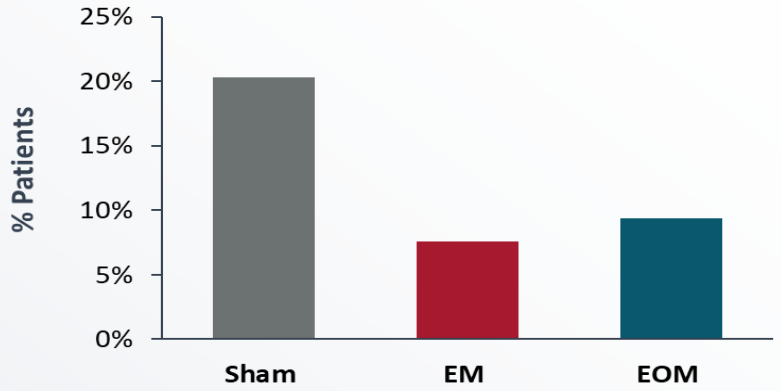
Patients with persistent BCVA ≥15-letter loss through month 12⁺



Nominal p-value vs sham^	---	0.0021	0.032

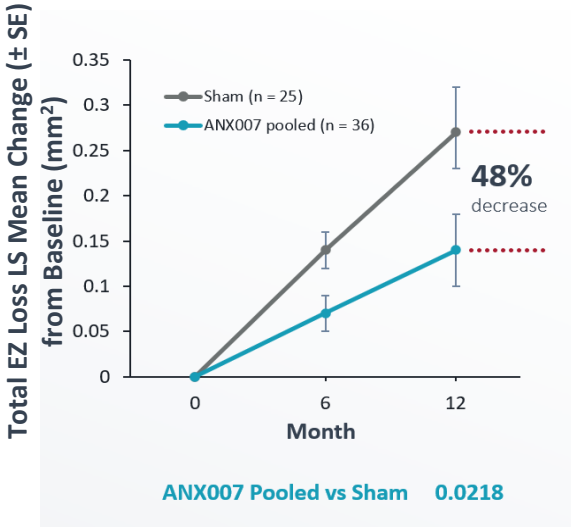
REDUCED RISK OF LLVA ≥15-LETTER LOSS

Patients with single LLVA ≥15-letter loss through month 12



- Dose-dependent response in reducing risk of loss of ≥ 15 BCVA AND LLVA LETTERS
- First known clinically meaningful preservation of vision in GA
- BCVA ≥15-letter loss universally deemed clinically meaningful

CHANGE IN TOTAL EZ LOSS AREA 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

⁺Persistent for two consecutive visits including month 12
^Nominal p-value from a Chi-square test in ITT population

EM: monthly dosing; EOM: every other month dosing

ANX007 Generally Well-Tolerated

ADVERSE EVENTS OF SPECIAL INTEREST n (%)	SHAM (N=89)	ANX007 EM (N=89)	ANX007 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

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

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

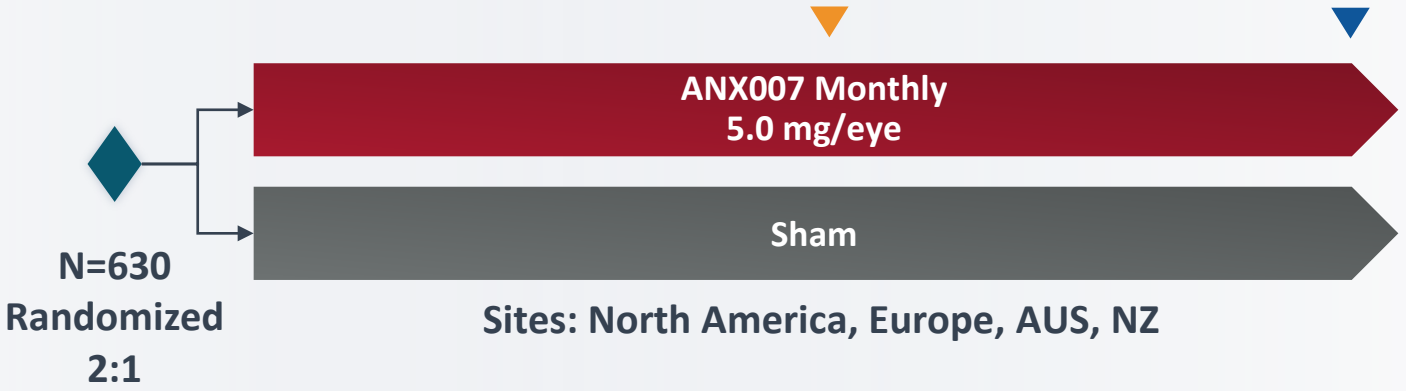
ARCHER II Phase 3 Program – Currently Enrolling

PRIME designation from EMA

ARCHER II TRIAL
Sham Study

Primary analysis: ~12 months*

Treatment masked through 24 months



PRIMARY ENDPOINT

Persistent BCVA ≥15-Letter Loss through ~12 months*

*Primary analysis based on accumulation of BCVA ≥15-letter loss target events assessed between months 12-18 from initiation of dosing

SECONDARY ENDPOINTS

Safety, Low Luminance VA (LLVA), Ellipsoid zone (EZ) integrity

Conclusions: C1q Inhibition

- **C1q Inhibition across several neurodegenerative diseases appears to convey protective effects resulting in functional benefit**
  - ANX005 met its primary endpoint in the phase 3 trial vs placebo on the GBS Disability Scale
  - 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 ANX007 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 is now enrolling with PRIME designation from EMA**