ANNEXON biosciences

GAME-CHANGING MEDICINES FOR COMPLEMENT-MEDIATED DISEASES

INVESTOR PRESENTATION

FEBRUARY 2023

Nasdaq: ANNX

Forward-Looking Statements

This presentation contains “forward-looking” statements about Annexon, Inc. and our industry that involve substantial risks and uncertainties. All statements other than statements of historical facts, including statements regarding our clinical and preclinical programs, timing and commencement of future nonclinical studies and clinical trials and research and development programs, timing of clinical results, strategic plans for our business and product candidates, including additional indications which we may pursue, our financial position, runway and anticipated milestones, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “aim,” “anticipate,” “assume,” “believe,” “contemplate,” “continue,” “could,” “design,” “due,” “estimate,” “expect,” “focus,” “goal,” “intend,” “may,” “objective,” “plan,” “positioned,” “potential,” “predict,” “seek,” “should,” “target,” “will,” “would” and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

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A bold mission to free the body, brain and eye from complement-mediated disease

Annexon Overview: On a Mission to Drive Significant Value

Pioneering Classical Complement Platform in Autoimmunity, Neurodegeneration & Ophthalmology

- Complement clinically / commercially validated with downstream approaches (C1s, C3, C5)
- ANNX building on prior learnings to block both up & downstream complement where it starts
  - Pursuing indications where (i) C1q localizes on disease tissue to anchor complement activation & (ii) complement activity drives disease progression
- Multi-faceted 'beach-head' portfolio with 'informed signal finding' and 'confirming' trials
- Clinical POC with lead drug candidate (ANX005) in multiple indications: GBS, HD, CAD, ALS

Significant 'Enterprise Value' Potential with multiple drivers over the next 3 years

- Targeting both Orphan and large patient population diseases with 4 Flagship Programs -- ~$10B market opportunity*
- Multiple expected value driving clinical readouts over 2023 & 2024, including GA & GBS efficacy trials
- Potential 1st-in-class GBS commercialization & initiation of potential 1st-in-class anti-complement HD pivotal trial
- Potential 1st-in-class oral compound for Autoimmune diseases

Well-Capitalized with Additional Opportunities

- Robust IP estate
- Wholly-owned with specific therapeutic-area partnering opportunities

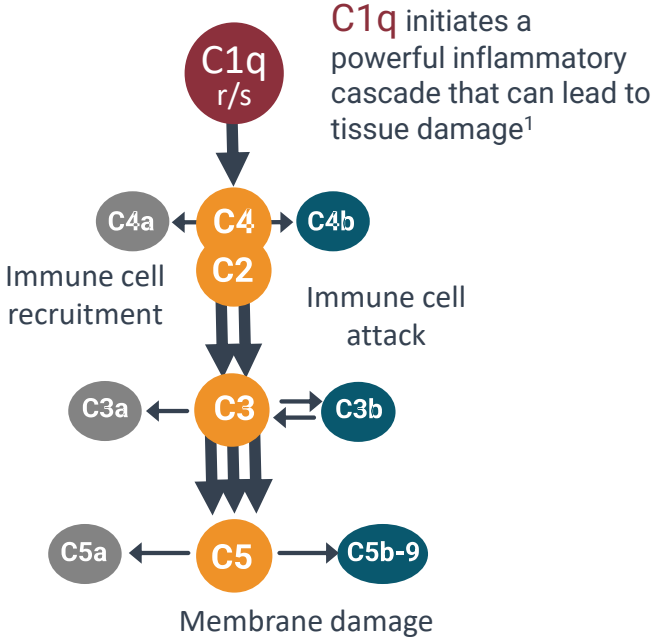
* Based on market data and company estimates

Revolutionizing Complement Biology in Pursuit of Our Mission

Targeting C1q & classical complement cascade to treat autoimmune and neurodegenerative disease

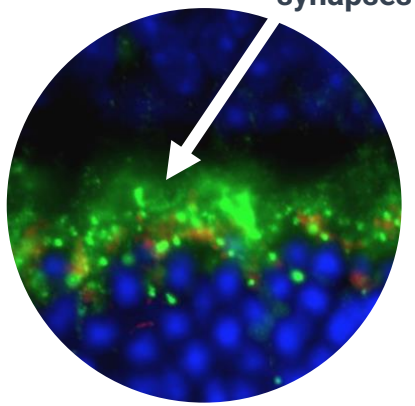
1960-70s — **2007** — **2014 - 2022** →

Understanding **C1q's role** in autoimmune disease



Discovery of C1q's role in **brain & eye neurodegeneration** by ANNX founder, Dr. Ben Barres

C1q anchors damaging complement activation on photoreceptor synapses in GA[2]



C1q Drives Removal of Functioning Synapses[3]

Annexon launched & advanced into mid- and late-stage trials targeting C1q-mediated diseases of the body, brain & eye

- ✓ **Validated role of C1q** in autoimmune & neurodegenerative disease
- ✓ **Full target engagement** with multiple drug candidates
- ✓ **Clinical POC in multiple diseases**
- ✓ **Well-capitalized** with runway into 2025
- ✓ **Talented 'Warrior Spirit' team**

[1]McGonigal et al. Acta Neuropathologica Communications (2016) 4:23 ; [2]C1q bound to photoreceptor synapses in aged mice: Annexon data on file; [3]Stevens, et al., 2007, Cell

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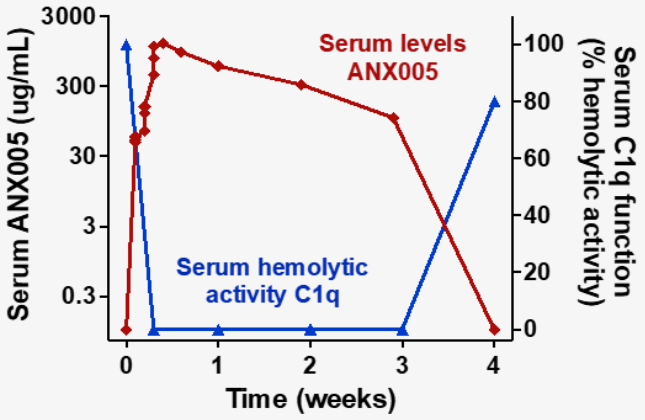
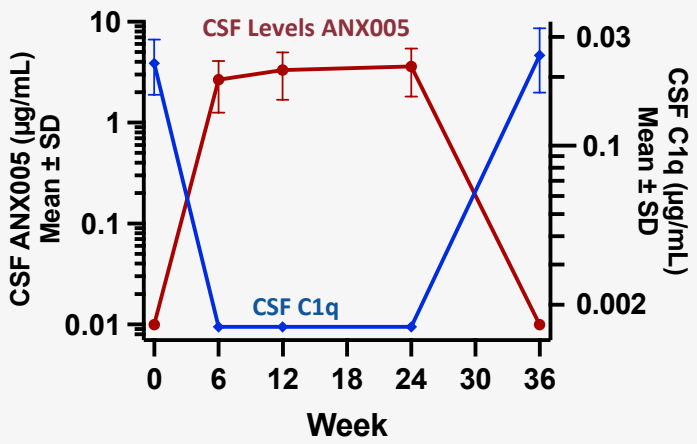
Robust Clinical Target Engagement of C1q Demonstrated in the Body, Brain & Eye

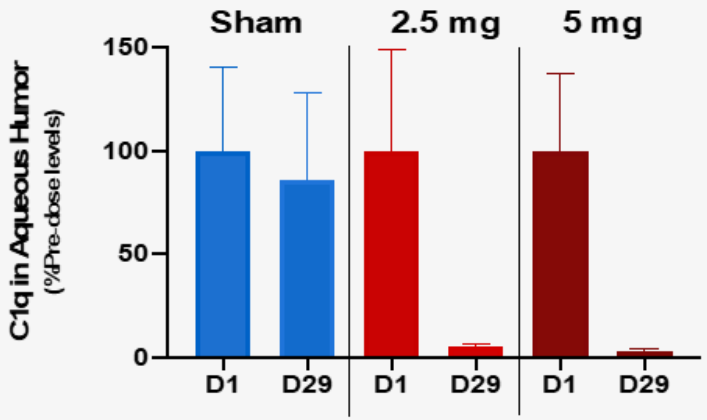
Full C1q Inhibition in Serum with ANX005



Full C1q Inhibition in CSF with ANX005



Full C1q Inhibition in Aqueous Humor with ANX007



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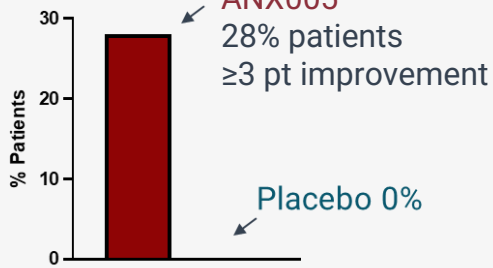
Clinical Proof-of-Concept Demonstrated in Both Autoimmune and Neurodegenerative Indications

Guillain-Barré Syndrome (GBS)

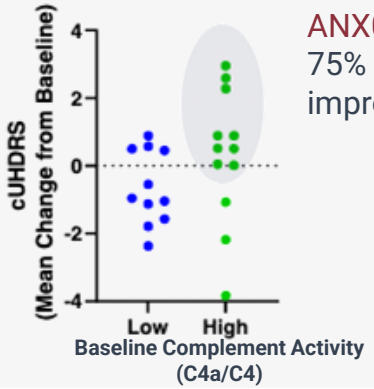
GBS 6-point disability scale:

1. Slight symptoms
2. Walk / no running
3. Walk with support
4. Bedridden / chair bound
5. Ventilator-assisted breathing
6. Death



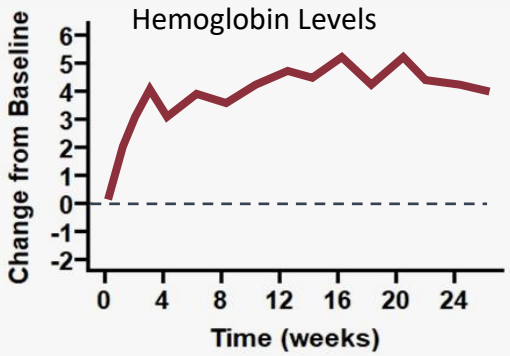
Huntington's Disease (HD)

Composite Unified Huntington's Disease Rating Scale



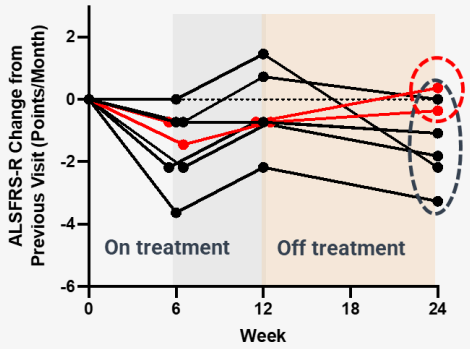
ANX005
75% patients improved

Cold Agglutinin Disease (CAD)



ANX005
Patient showed >2 pt improvement

Amyotrophic Lateral Sclerosis (ALS)



ANX005
All patients improved or maintained progression rate during treatment

Both patients that stayed on drug continued to improve

All patients who went off treatment declined

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Achieving Our Mission With **FOUR FLAGSHIP PROGRAMS**

Stopping Harmful Inflammation and Tissue Damage in the Body, Brain & Eye

Guillain-Barré Syndrome (GBS)

AUTOIMMUNE

Well-validated MOA
Fast path to market in rare disease

1st placebo-controlled trial in ~40 years

Huntington's Disease (HD)

NEURODEGENERATION

Pioneering MOA
No disease-modifying treatments available

1st complement inhibition in a brain disorder

Geographic Atrophy (GA)

OPHTHALMOLOGY

Well-validated MOA
Localized inhibition in eye

1st up & downstream complement approach

Oral Small Molecule

AUTOIMMUNE

Well-validated MOA
Potential ease and convenience of oral dosing

1st oral compound targeting classical complement

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Flagship Programs Advancing in Mid-stage and Pivotal Trials

INDICATION	CANDIDATE	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	2023 ANTICIPATED MILESTONES
Guillain-Barré Syndrome	**ANX005**					Complete Phase 3 enrollment in 2H 2023
Huntington's Disease	**ANX005**					Initiate Phase 2/3 trial 2023
Geographic Atrophy	**ANX007**					Report Phase 2 data mid-2023
Autoimmune Indications	**ANX1502**					Complete MAD trial and initiate POC trial in patients




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Flagship Programs

- Guillain-Barré Syndrome (GBS)
- Huntington’s Disease (HD)
- Geographic Atrophy (GA)
- Oral small molecule

ANX005 Designed to Powerfully Inhibit C1q and Entire Classical Complement Pathway in the Body and Brain

Key Attributes

- ✓ **Diverse**: Utilized in autoimmune & neurodegenerative trials
- ✓ **Potency:** High binding affinity to C1q (<10 pM)
- ✓ **Target Engagement:** Full C1q inhibition observed in blood and CSF
- ✓ **Safety Results:** Generally well-tolerated in acute and chronic trials
  - ✓ No drug-related deaths & no serious infections observed
  - ✓ No autoimmune events observed post enhanced ANA screening / monitoring
- ✓ **Clinical:** Rapid clinical benefit demonstrated in GBS, HD, CAD & ALS

Administered to >200 patients to date

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ANX005 Generally Well-Tolerated in Several Patient Populations

KEY TAKEAWAYS

Leveraged learnings to optimize safety profile

- Low grade, transient IRRs during first infusion: managed by infusion rate and pre-medication
- Single serious event of autoimmunity (SLE/ lupus-like syndrome): no further events of autoimmunity observed post enhanced ANA screening / safety monitoring to date

No drug related deaths & no serious infections observed throughout all studies to date

6 completed and 2 ongoing acute and chronic autoimmune & neurodegenerative trials

- >100 patients from completed trials
- >110 patients in ongoing trials
- Exposure up to 1 year

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ANX005 Generally Well-Tolerated Across Clinical Trials

Treatment Emergent Adverse Events (TEAE)	Safety Population (N=116*)	
	All CTCAE Grades N (%)	CTCAE Grade ≥3 N (%)
Any reported TEAEs, N (%)	114 (98.3)	29 (25.0)
Most Common TEAE, N (%)		
Infusion Related Reaction (IRR)	38 (32.8)	3 (2.6)
Most Common TEAEs (non-IRR), N (%)		
Headache	37 (31.9)	0 (0)
Pain in extremity	24 (20.7)	0 (0)
Rash**	26 (22.4)	2 (1.7)
Pyrexia	18 (15.5)	0 (0)
Lab abnormality - CPK	15 (12.9)	6 (5.2)
Constipation	13 (11.2)	0 (0)
Pruritus	13 (11.2)	0 (0)
Serious TEAEs, N (%)	9 (7.8)	8 (6.9)
Related to ANX005	3 (2.6)	3 (2.6)
Infections	0 (0)	0 (0)

Study Deaths and Serious Adverse Events

- No deaths and no serious infections observed
- 3 observed serious adverse events related to ANX005
  - 1 IRR in NHV prior to dosing optimization
  - 2 in HD P2a trial (lupus like syndrome and idiopathic pneumonitis) prior to implementation of ANA screening and safety monitoring plan

Adverse Events of Note

- Infusion Related Reactions (IRR) primarily first dose effect across indications (~95%) and commonly associated with transient rash
  - Adverse events coded as rash were primarily IRR
  - No IRR observed after 2nd dose of ANX005
- Elevated creatine phosphokinase (CPK) seen in placebo and ANX005 treated GBS patients – consistent with GBS

* All completed and open label studies with ANX005 (data cutoff 10/8/22); Includes: FIH, GBS P1b, GBS DDI, HD P2a, ALS P2a, CAD P2, wAIHA P2 trials
** Primarily initial dose IRRs, but coded under preferred term rash

Potential First-In-Class Treatment for GBS

Acute, antibody-mediated autoimmune disease driven by aberrant C1q activation

GBS Overview

Rapid onset of **neuromuscular weakness** and paralysis

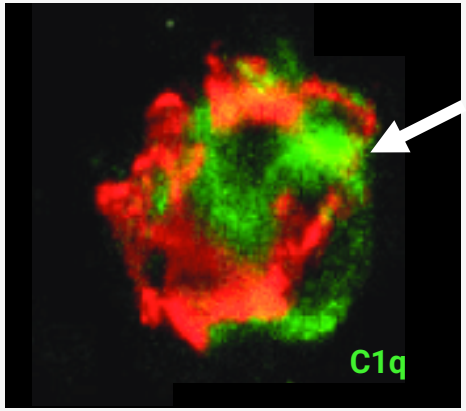
12,000 patients diagnosed/year in North America & Europe

No FDA-approved therapies

Role of C1q

C1q binds autoantibodies on nerve components, anchoring complement activation, inflammation & tissue damage

ANX005 blocks all inflammatory / damaging components of classical pathway for rapid recovery



C1q targeting the neuromuscular junction

ANX005

- ✓ Fast Track & Orphan Drug Designations
- ✓ Pursuing monotherapy label
- ✓ **Phase 3 pivotal trial ongoing**
- ✓ **Productive engagement with FDA on the statistical analysis plan for the ongoing pivotal trial**

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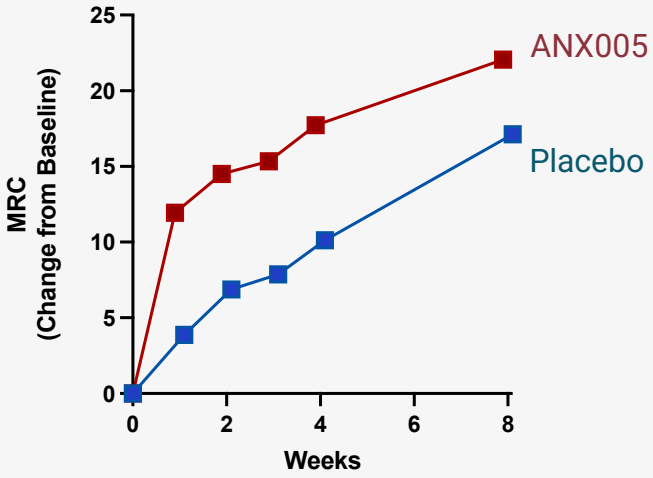
ANX005 Demonstrated Clinical POC in GBS Placebo-Controlled Trial

Early improvement in muscle strength and reduction in neuronal damage preceding gain of function

Impact on Muscle Strength

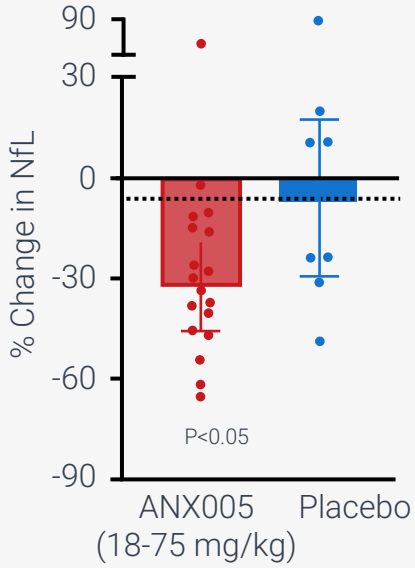
Rapid increase in muscle strength within first week of treatment



Mean Change in MRC Score from Baseline

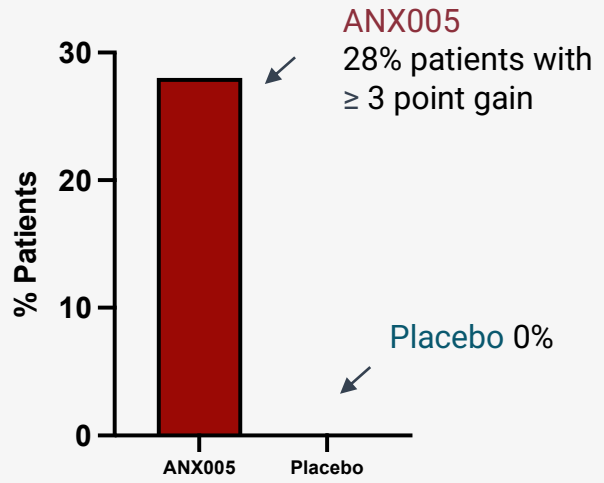
Impact on Key Neuronal Biomarker

Statistically significant early NfL reduction (weeks 2-4)



Impact on Clinical Function

Patients achieving ≥3 point improvement in 8 weeks



Guillain-Barré
6-Point Disability Scale

All graphs: ANX005 n=18, Placebo, n=8

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ANX005 GBS Phase 3 Pivotal Trial Underway

On track to complete expanded enrollment in 2H23 with Phase 3 data expected in 1H24

Trial Design*

Specifications*

- **Randomized, double-blind trial (N~220)**
- Recently diagnosed severe patients (3 or higher on GBS-DS)
- **Primary endpoint: GBS Disability Scale at week 8**
- Patients stratified for baseline muscle strength and time from symptom onset
- **Productive engagement with FDA on the statistical analysis plan for the ongoing pivotal trial**
  - **Increased study population by ~40 patients**

*Pending planned protocol amendment

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Potential First-In-Class Treatment for HD

Progressive neurodegenerative disease involving excessive synapse loss and neuronal damage

HD Overview

Progressive, inherited neurodegenerative disorder

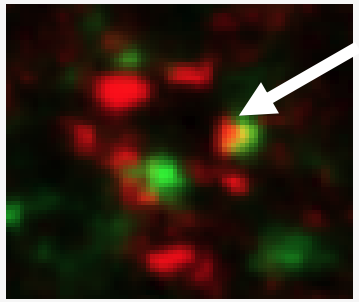
80K people affected globally; ~300K at-risk[1]

No approved treatments that reverse or slow disease progression

Role of C1q

C1q triggers synapse damage, synapse removal and neuroinflammation [2,3]

ANX005 blocks classical complement activation to protect synapses, reduce neuroinflammation and improve clinical outcomes



C1q targeting synapses on striatal neurons of HD patient[3]

ANX005

- ✓ Phase 2 results demonstrated positive clinical outcomes
- ✓ Orphan Drug Designation
- ✓ **Productive engagement with FDA**
- ✓ **Pivotal trial design aimed at slowing rate of disease progression**
- ✓ **Phase 2/3 trial expected to initiate in 2023**

[1]1GlobalData and market research reports, [2]Wilton 2021 doi.org/10.1101/2021.12.03.471180; [3]Hong 2016 *Science* doi 10.1126/science.aad8373; Stevens 2007 *Cell* doi 10.1016/j.cell.2007.10.036; Fonseca, 2004, *J Neurosci*; Dejanovic, 2018, *Neuron*; Vukojicic, 2019, *Cell Reports*; Howell, 2011, *J Clin Inves*; Williams, 2016, *Mol Neurodegen*; Jiao, 2018, *Mol Neurodeg*; Lui, 2016, Cell **165**:921; Krukowski, 2018, Int.*JMol Sci*; Holden, 2021, *Science*; Annexon NfL reduction in SOD1 model, unpublished; Absinta, *Nature*, 2021

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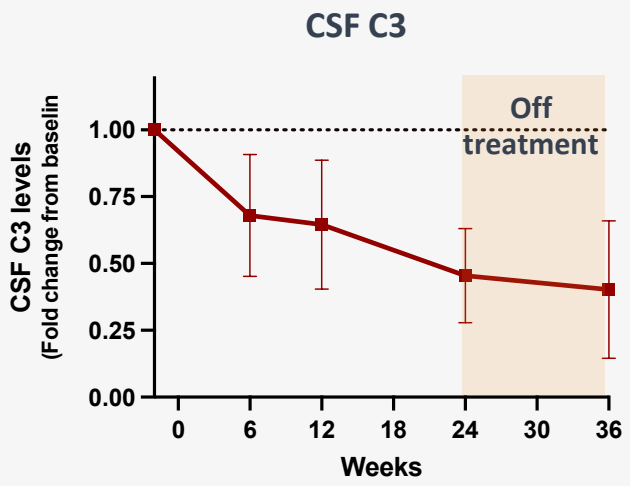
ANX005 Improved Clinical Outcomes in HD Phase 2 Trial

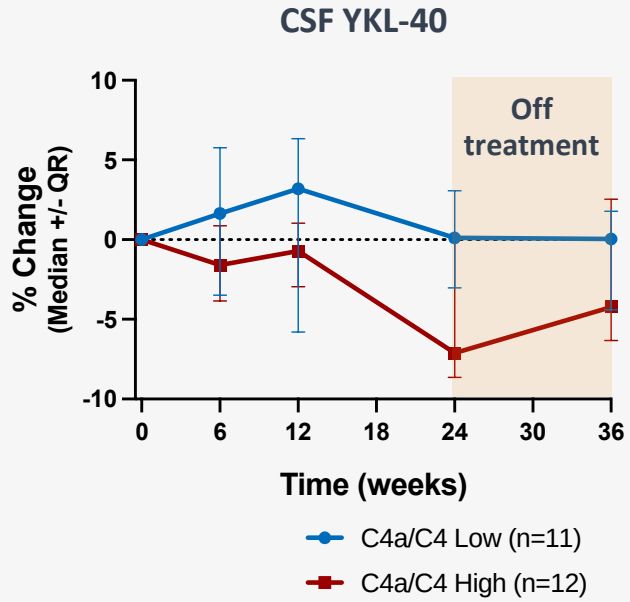
Reduced Downstream Complement

CSF C3 levels decreased in all patients during on and off treatment period



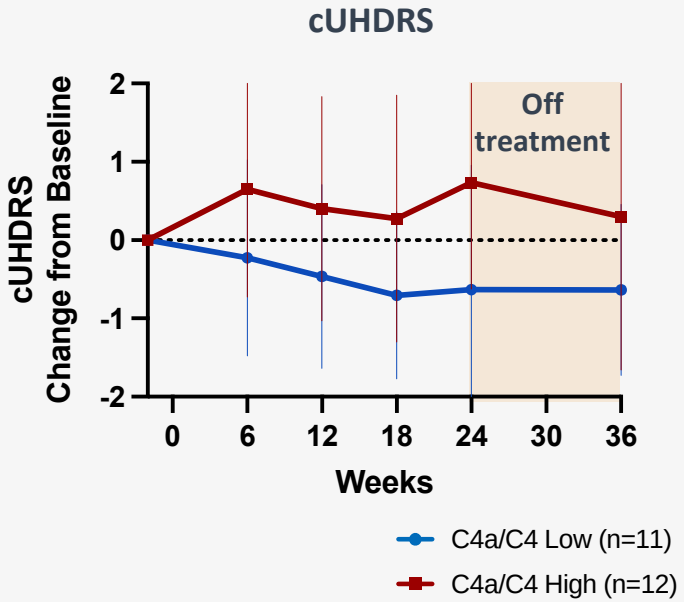
Reduced Neuroinflammation

HD inflammation marker (YKL-40*) reduced in patients with high baseline complement activity (C4a/C4)



Improved Clinical Function

Benefit at all time points in high complement group (cUHDRS)



*Produced by activated glia - Elevated in HD and other neurological diseases

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ANX005 Pivotal Phase 2/3 HD Trial Expected to Initiate in 2023

Trial Design

- Randomized, double-blind, placebo-controlled
- **Leveraging precision medicine approach** for patients with elevated baseline complement levels

Patient Population

- **Patients with manifest and pre-manifest HD**
- CAP score > 400
- UHDRS independence score ≥ 80

Key Objectives

- **Disease progression** measured by cUHDRS and TFC
- **Confirm observations with rapid drug impact on high complement baseline patients**
- Patient motor, cognition, behavior, functional capacity and quality of life assessments
- Safety and tolerability of ANX005

EXPECT TO INITIATE PHASE 2/3 IN 2023

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Potential First-In-Class for Early Complement Inhibition in GA

Progressive neurodegenerative retinal disease involving C1q-driven synapse and photoreceptor loss

GA Overview

Leading cause of blindness in the elderly

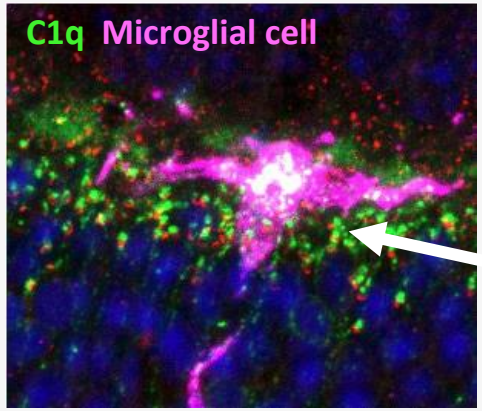
1M people diagnosed in US; 5M people globally

Current approaches target downstream complement

Role of C1q

C1q drives tissue damage in the retina by anchoring complement activation on drusen, photoreceptor cells and synapses

ANX007 has potential to provide more complete protection by shutting down all classical pathway components



C1q directing synapse engulfment by microglial cells[1]

ANX007

- ✓ Targeting up and downstream complement activation
- ✓ Aim to slow rate of lesion growth
- ✓ Fast Track Designation
- ✓ **Administered to 200 patients to date**
- ✓ **Phase 2 data anticipated mid-2023**

[1]Annexon data on file

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ANX007 Designed to Powerfully Inhibit C1q & Classical Pathway in All Layers of the Retina

Key Attributes

- ✓ **Potency: <10 pM** Fab antibody formulated for intravitreal administration
- ✓ **Target Engagement:** Complete C1q inhibition in the eye for at least 4 weeks
- ✓ **Safety Results:** Generally well-tolerated in Phase 1b trial
- ✓ **Preclinical Data:** Demonstrated protection of photoreceptor cells and retinal function
- ✓ **Dosing:** Pharmacokinetics in patient aqueous humor supports monthly/every other month dosing; optimizing formulation for less frequent dosing

Administered to 200 patients to date

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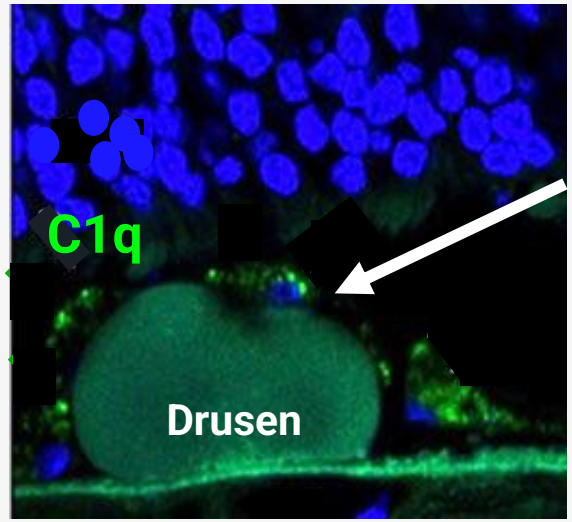
Targeting C1q's Dual Role in Vision Loss in GA

C1q drives inflammation in retina and specific mechanism of synapse loss on photoreceptor neurons

C1q Well Positioned to Drive Retinal Damage

C1q localized on drusen (hallmark pathology of GA)

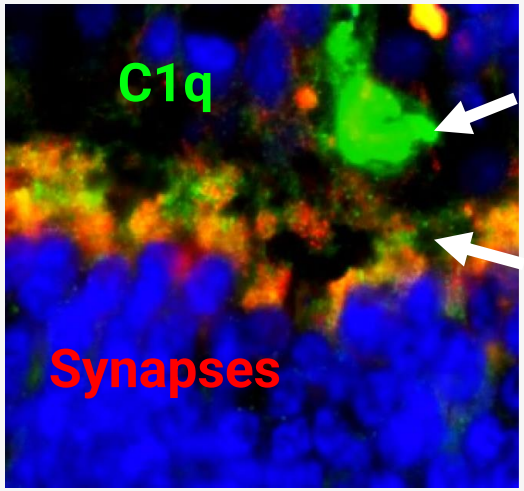


Modified Image from Jiao, 2018

C1q anchors classical complement activation on drusen

C1q's Unique Role in Neurodegeneration

C1q tags photoreceptor synapses to drive inflammation and neuronal damage



Activated microglial cells engulf synapses

C1q guides microglial cells to target synapses in GA

C1q initiates & propagates neuroinflammation in the retina

Retina specimens from GA patients were procured from the San Diego Eye Bank; Annexon data on file; Tassoni et al, IOVS 2022 (ARVO Abstract)

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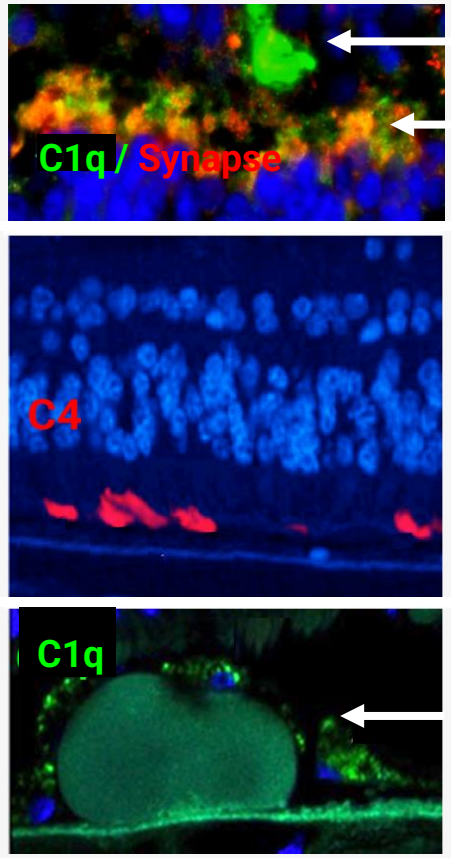
Broader Overview of C1q's Role in GA Progression

C1q accumulates in all layers of the outer retina and positioned as key driver of complement activation

- Drusen contain activating C1q substrates
- **C1q activation / inflammation contributes to retinal damage**
- Microglia/macrophages infiltrate the retina, expressing more C1q
- **C1q directly recognizes components of photoreceptor neurons → cell damage**
- **C1q tags photoreceptor synapses on stressed neurons → synapse pruning / degeneration**

GA Retinal Tissue



C1q-expressing microglial cell[1]

C1q on photoreceptor synapses[1]

C4, downstream of C1q, on photoreceptor cells at leading edge of pathology[2]

C1q on and around drusen[3]

[1]Annexon data on file; [2]Katschke, 2018; [3]Jiao, 2018

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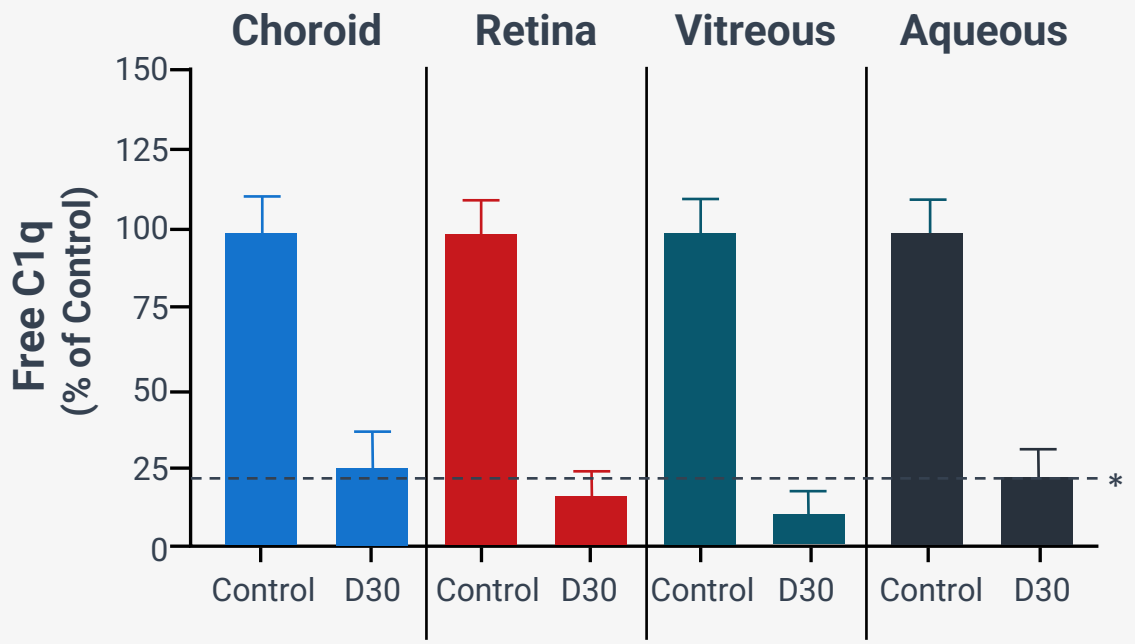
ANX007 Inhibits C1q Throughout the Retina

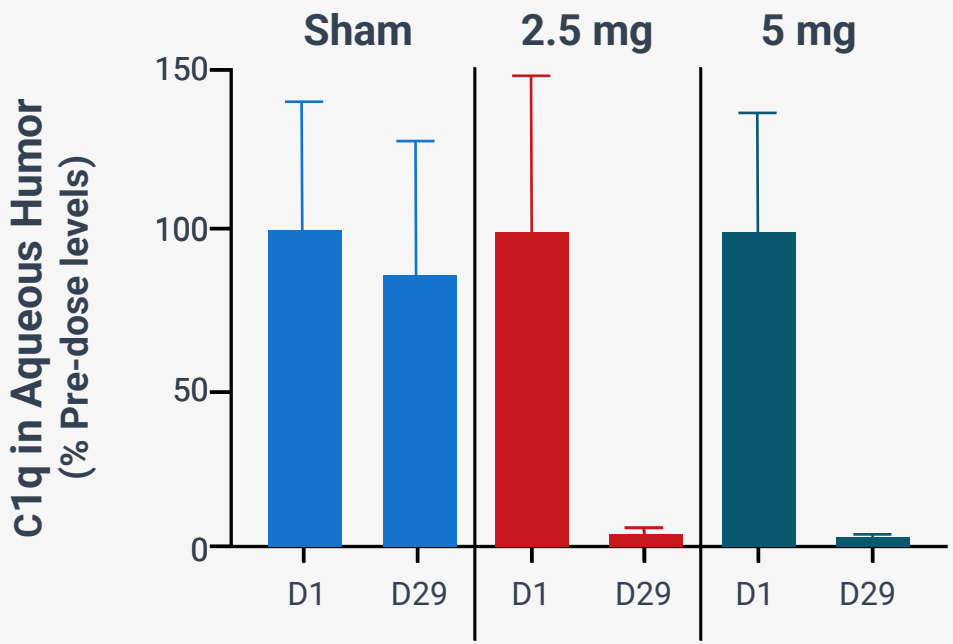
C1q Occupancy by ANX007 Following Intravitreal Administration in Primates



D30 = Day 30 (30 days post-2nd ANX007 dose)

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

C1q Occupancy by ANX007 In Patient Aqueous Supports Monthly/Every Other Month Dosing



D1 = Day 1 (before ANX007 dosing)

D29 = Day 29 (post-1st dose)

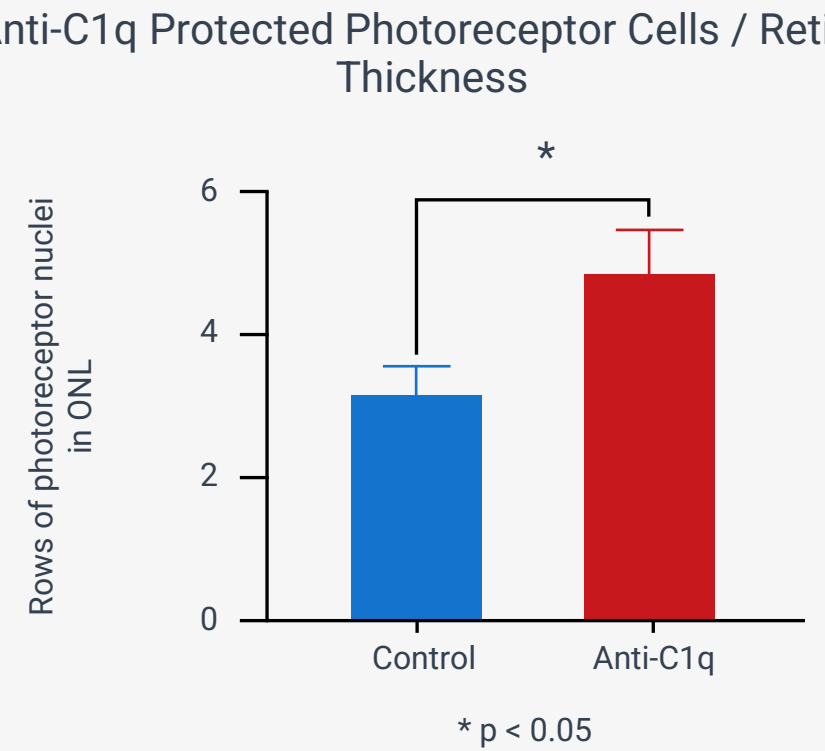
*Within resolution limits of assay

Grover et al, IOVS (in press); Sun et al, AAO Annual Meeting 2020; Annexon Data on File

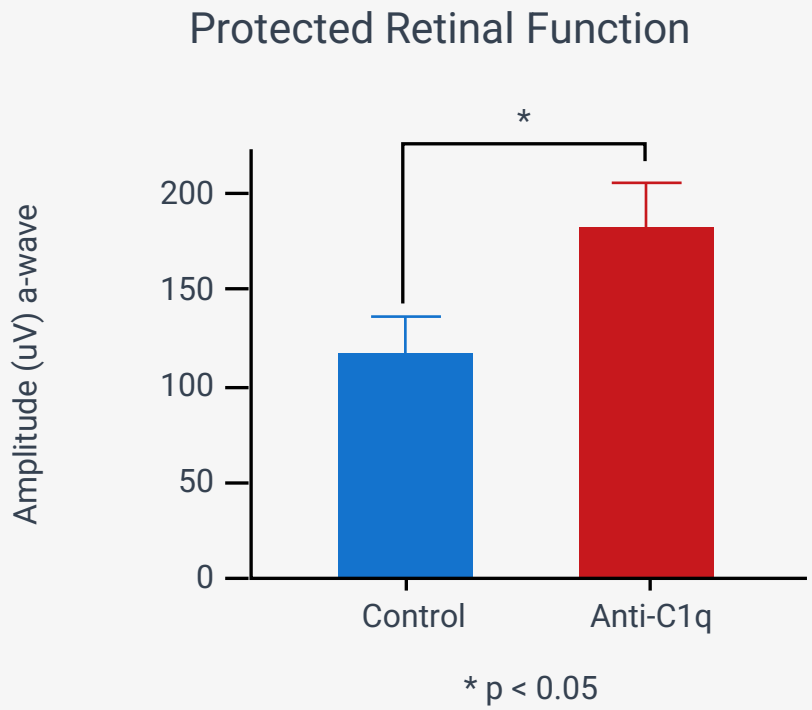
ANNEXON biosciences

Blocking C1q Protected Photoreceptor Structure and Function in Mouse Light Damage Model

Protection of Retinal Layer Thickness / Cell Number



Protection of Photoreceptor Cell Function

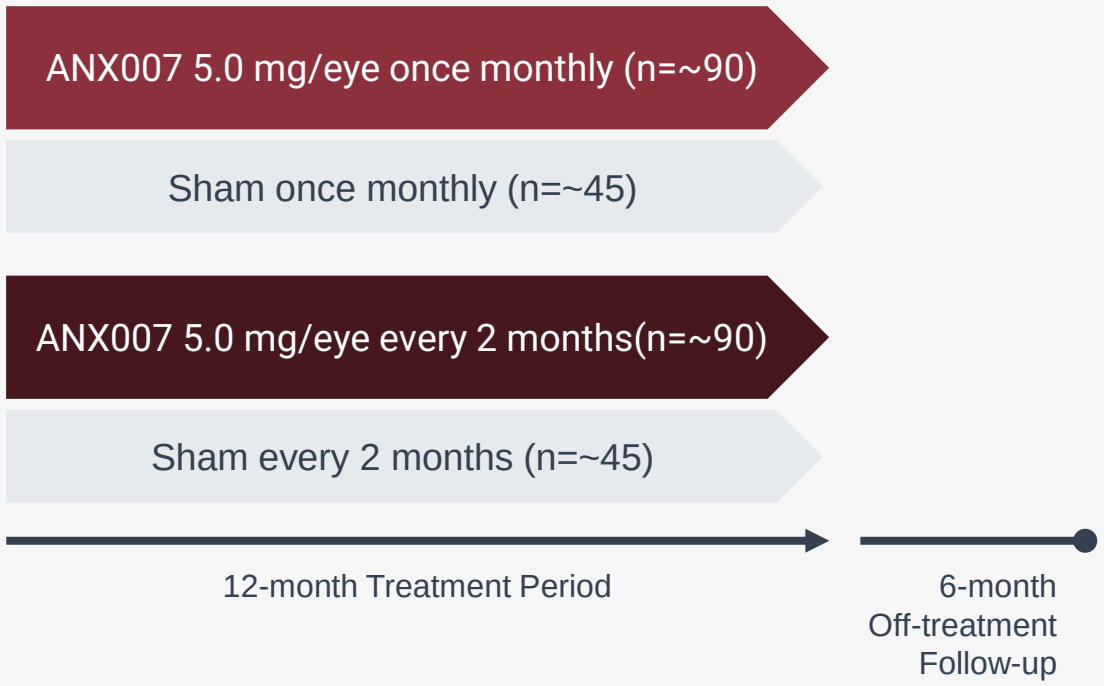


Jiao, 2018

ANNEXON biosciences

Ongoing ANX007 Phase 2 GA Trial with Data Expected Mid-2023

ARCHER Trial Design



Specifications

- Randomized, double-masked, sham-controlled trial **(N~270)**
- **Patients stratified based on lesion size and location (>45% patients with non-foveal lesions)**
- Primary endpoint: Rate of change (slope) in GA lesion area assessed by fundus autofluorescence (FAF)
- **>50% of patients through 12-month treatment period with >90% adherence with office follow-ups***

PHASE 2 DATA EXPECTED MID-2023

* As of December 8, 2022

ANNEXON biosciences

ANX1502: First Oral, Small Molecule Designed for Classical Complement-Mediated Autoimmune Diseases

Opportunity

Autoimmune indications with strong scientific rationale, including:

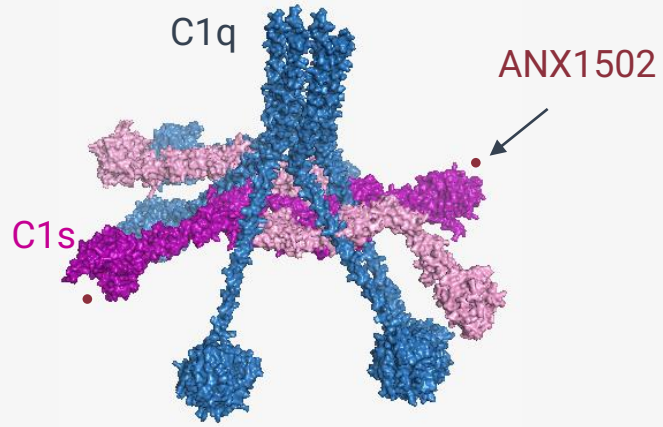
- Multifocal motor neuropathy (MMN)
- Lupus Nephritis
- Myasthenia gravis
- Cold agglutinin disease (CAD)

Role of C1s

Targeting active form of C1s responsible for classical pathway activation

Potent and selective inhibitor of C1s (serine protease): selective over related proteases (200 – 50,000-fold)

Highly specific for classical pathway



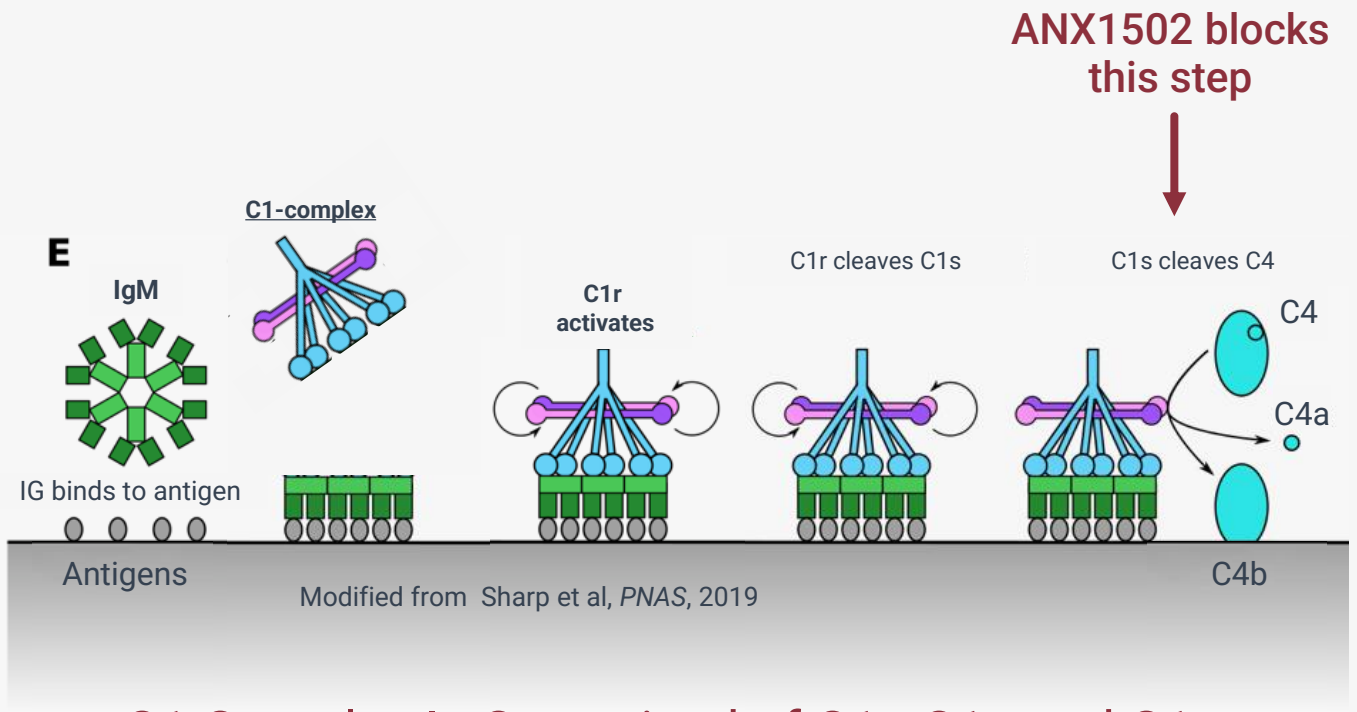
ANX1502

- ✓ **Orally administer** for chronic therapy in several diseases
- ✓ **Achieved target drug levels** in on-going Phase 1 SAD trial
- ✓ **Conducting MAD in healthy volunteers**
- ✓ **Expect to initiate POC in 2023**

ANNEXON biosciences

Following C1q Binding to a Surface, ANX1502 Inhibits Activated C1s

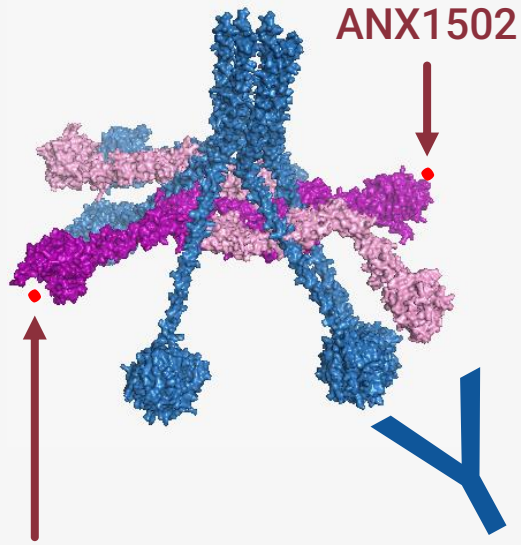
Structure of C1-complex bound to IgM-antigen on a surface



C1 Complex Is Comprised of C1r, C1s and C1q

Sharp et al, *PNAS*, 2019

Structure of unbound C1-complex



ANX1502 binds to C1s catalytic site to inhibit enzymatic activity (MW ~300 D)

Anti-C1q (e.g., ANX005) binds to globular heads to block C1q binding (MW ~150,000 D)

Mortensen et al, *PNAS*, 2017

ANNEXON biosciences

ANX1502: Structure-Based Screening and Design

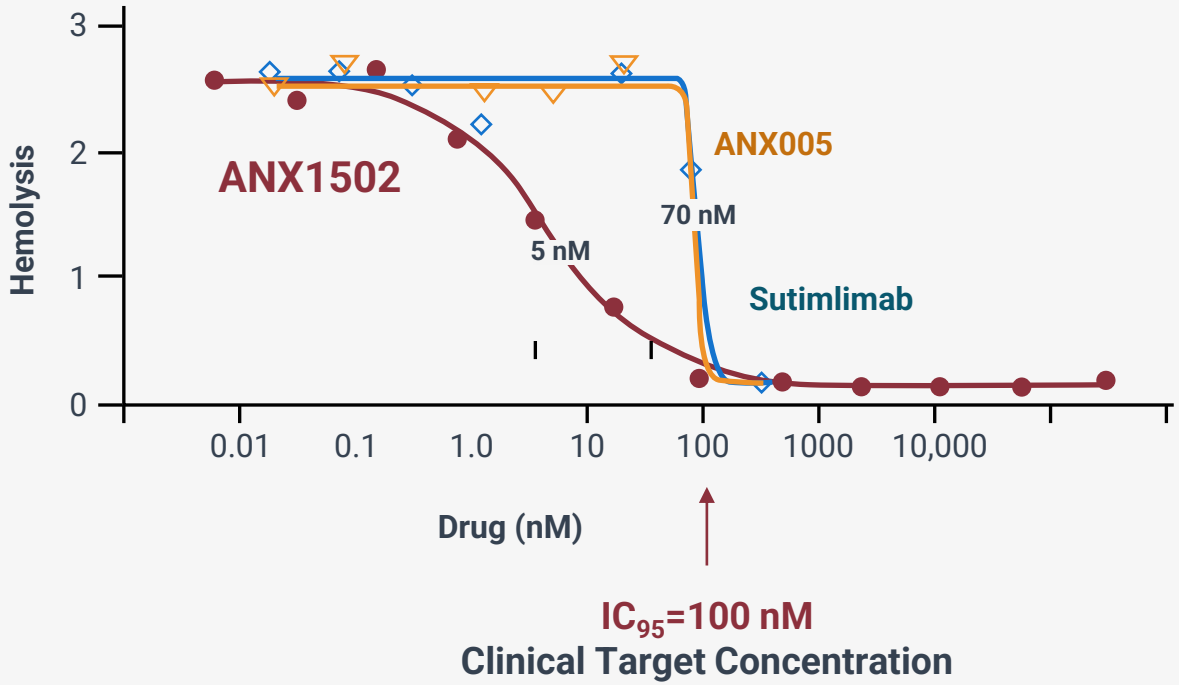
ANX1502 Discovery From HTS To CTA Submission

ANNEXON biosciences

ANX1502: Highly Potent and Selective Inhibitor of C1s

- **High affinity C1s:** 0.6 nM (Biacore)
- **Potent inhibitor:** 1 nM purified enzymatic assay
- **Selective** over related serine proteases (200 – 50,000-fold)
- **Robust functional inhibition** of classical pathway (comparable to sutimlimab)
  - *In vitro* hemolysis assay (IC_{50} = 5 nM)
  - Clinical target concentration =100 nM

Potent for *In Vitro* Hemolysis in Human Serum



ANNEXON biosciences

ANX1502 Well-Tolerated in Ongoing Phase 1 SAD Trial; Pharmacokinetic Results Support Twice Daily Dosing

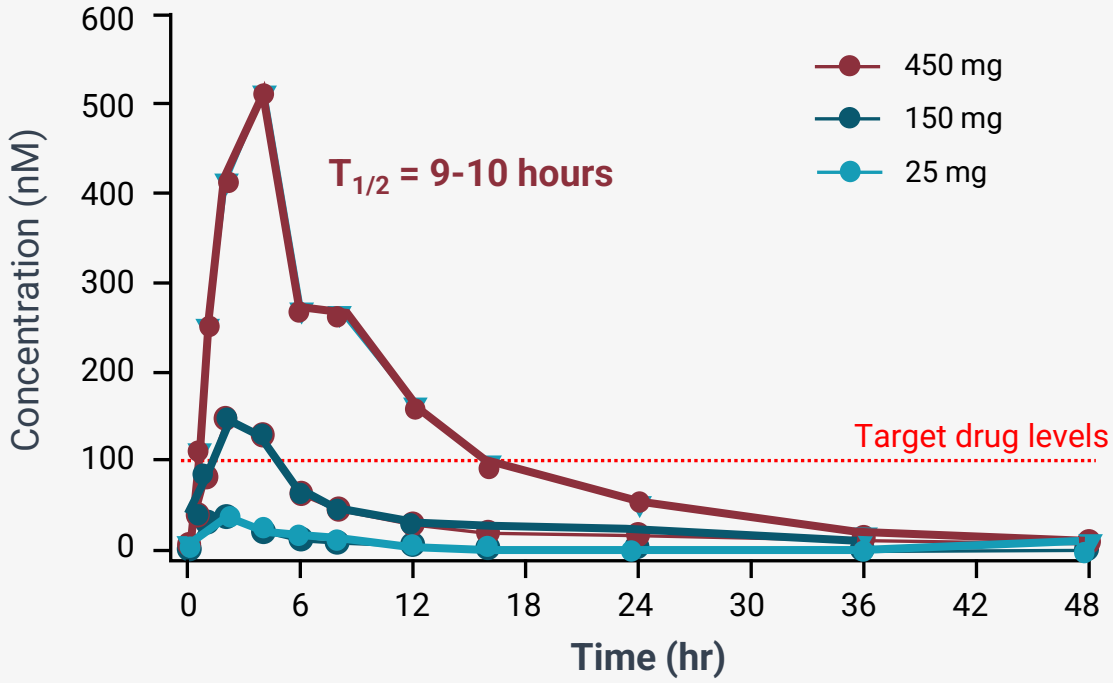
Safety Results*

- **ANX1502 generally well-tolerated**
- **Maximum tolerated dose not yet reached**
- All treatment-emergent adverse events (TEAEs) mild or moderate
- **No serious adverse events (SAEs)**
- No significant clinical/lab findings (e.g., liver enzymes, serum chemistry, hematology)

Single Dose of 450mg Achieved Target Drug Levels

450mg dose achieved >100 nM for 12 hours, supports twice daily dosing

Plasma levels after single dose**



- As of October 23, 2022
- **Cohorts where ANX1502 was administered without food

ANNEXON biosciences

ANX1502 Advancing Into Multiple Clinical Trials for Development in Autoimmune Indications

ANX1502 Development Plan

- **Complete Phase 1 SAD / MAD** study in healthy volunteers
  - Establish dose for patient studies

Phase 1 data expected 2023

- **Demonstrate rapid POC in CAD**
  - Establish 1502 PK/PD in a short duration trial with objective readout

POC trial initiation expected 2023

- **Expand autoimmune franchise into multifocal motor neuropathy (MMN)**
  - Strong scientific rationale; supporting data from mechanistically-related GBS indication

P2 trial initiation expected 2024

Next Steps for Program Expansion

- Additional franchise expansion informed by emerging data 2H23
  - Ph 1b LN data expected in 1H23; informs late-stage trial related diseases
  - Ongoing assessment of Myasthenia gravis (MG) and other indications

Expansion expected 2H23

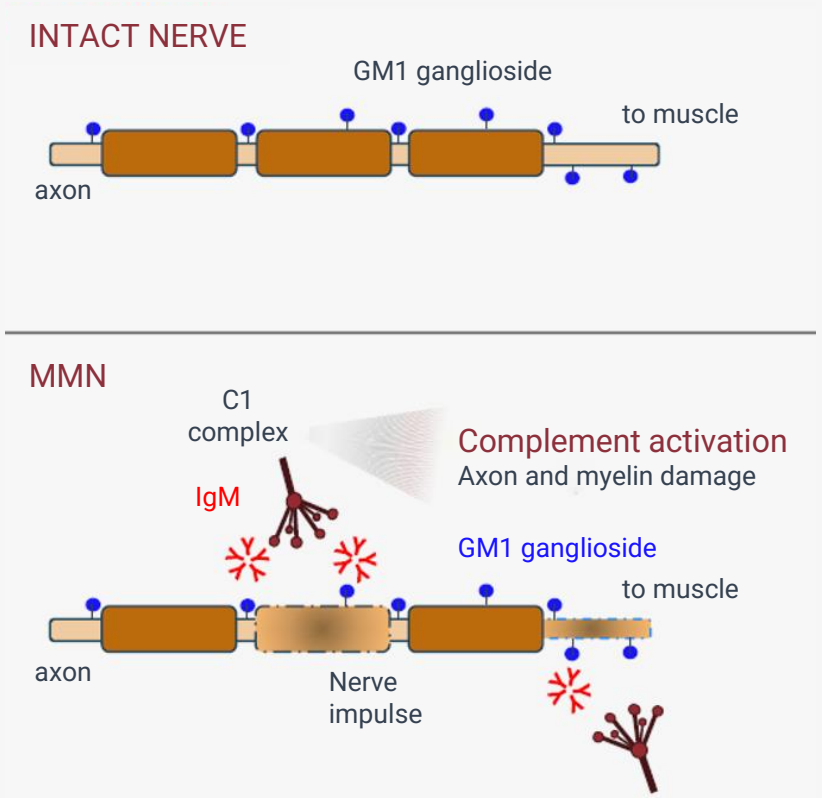
ANNEXON biosciences

MMN: Progressive Disability Despite Treatment With Standard Therapy

Disease Overview

- **Clinical features**
  - Slowly progressive asymmetrical distal limb weakness
  - Muscle wasting over time
- **Patients**
  - ~12K in US / EU
  - Commonly middle-aged men
- **Pathophysiology**
  - Anti-GM1 antibodies
  - Motor conduction block
- **Treatment**
  - Treated with IVIg, but progressive nerve damage continues
  - Life-long and time-consuming treatment

Nerve Damage Mediated by Classical Complement in MMN



National Organization for Rare Diseases
https://rarediseases.org/rare-diseases/multifocal-motor-neuropathy/
Vlam, Lotte et al., Neuroimmunology Neuroinflammation, 2015

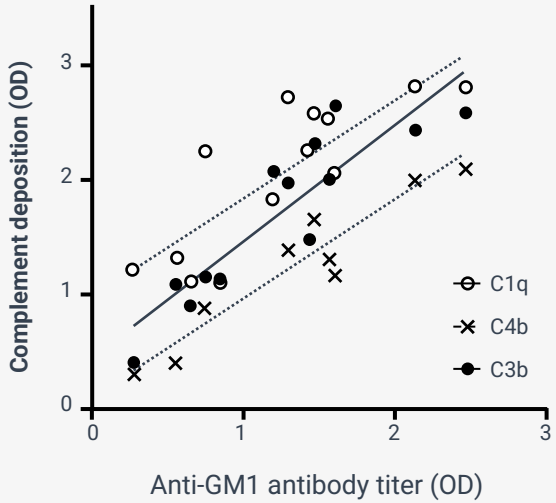
ANNEXON biosciences

Strong Rationale for C1 Inhibition as Therapy for MMN

IgM driven disease related to GBS

Classical Complement Activation in MMN

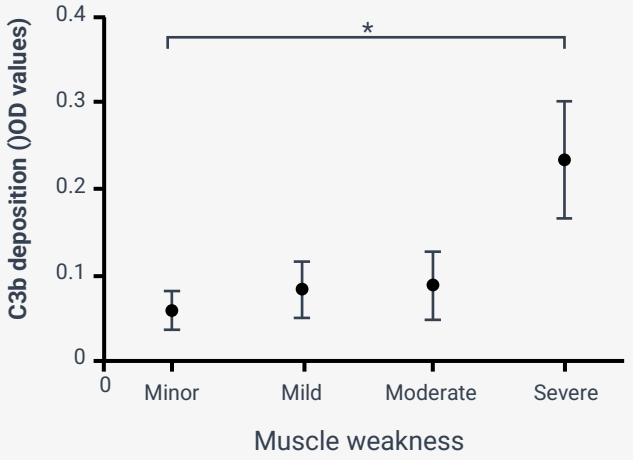
Patient sera: C1q, C4b and C3b deposition on GM1 ganglioside *in vitro* correlates with anti-GM1 IgM titers



Yuki, et al., J Neurol Neurosurg Psychiatry 2011

Complement Activation Correlates with Severity

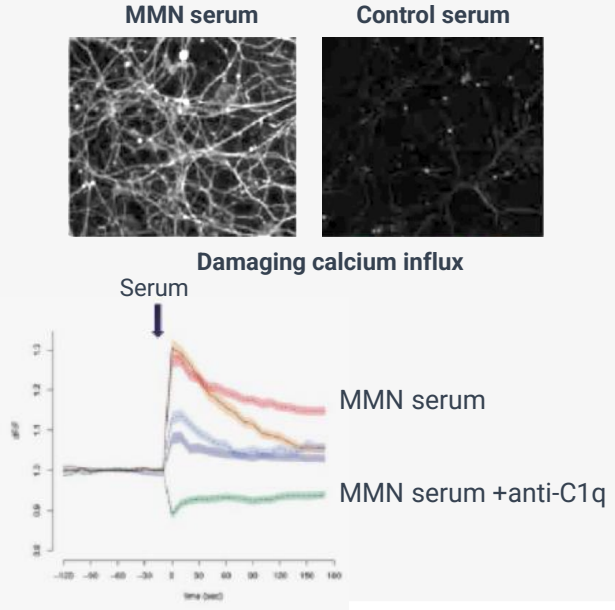
Patient sera: *In vitro* complement deposition on GM1 ganglioside correlates with MMN disease severity



Vlam, et al., Neurology 2015

C1 Inhibition Reduces Effect of MMN Antibodies

Neuronal culture: Anti-C1q blocks neurotoxic calcium influx caused by IgM GM1antibodies



Harschnitz, et al., Annals Neurol 2016

ANNEXON biosciences

Early Plans for MMN Study With ANX1502

Trial Design

- **Randomized, double-blind trial** assessing efficacy of ANX005 vs. IVIg
- IVIg rescue provided

Target Patient

- "Early" MMN and documented response to IVIg (run-in period)

Key Objectives

- Safety and tolerability
- **Confirm first use of oral drug candidate in MMN patient population**
- **Measures of peripheral muscle strength** using MRC sum score and hand-held dynamometry
- **Patient function**
- Need of IVIg retreatment

TIMELINE: INITIATE IN 1H 2024

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Additional Near-Term Opportunities

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Numerous Opportunities with Next Wave Programs

INDICATION	CANDIDATE	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	2023 ANTICIPATED MILESTONES
Amyotrophic Lateral Sclerosis (ALS)	**ANX005**					Report Phase 2 data in 2023
Lupus Nephritis (LN)	**ANX009**					Report Phase 1 data in 1H 2023
Autoimmune/ Neuro	**ANX105**					Report Phase 1 data in 2023

ANNEXON biosciences

Potential First-In-Class Treatment for ALS

Targeting up & downstream complement activity in both the brain and peripheral nerves

ALS Overview

Rapidly progressing neurodegenerative disorder (fatal within 3-5 years from diagnosis)

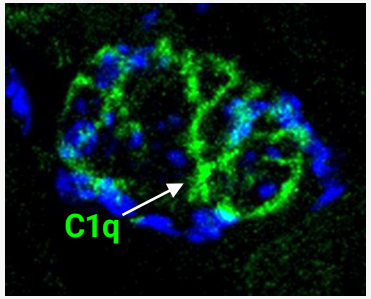
Affects **~19,000 people each year** in the US

Role of C1q

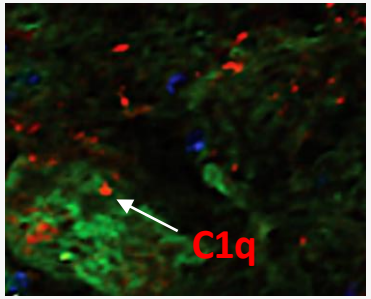
C1q targets both central and peripheral nerve components – motor neurons (MN) and peripheral neuromuscular junction (NMJ)[1, 2, 3]

C1q activation drives inflammation and neurodegeneration[1,2]

ANX005 blocks all downstream components of classical cascade **to prevent tissue damage**



C1q on NMJ[4]



C1q on central motor neurons[3]

ANX005

Differentiated, targeting both central and peripheral nervous system

Aim to slow rate of disease progression

Phase 2a trial actively enrolling, data expected 2023

Open-Label Treatment Period	Off-Treatment Period
3-6 Months[1]	3 months

[1]Protocol amendment extended treatment period from 3 months to 6 months

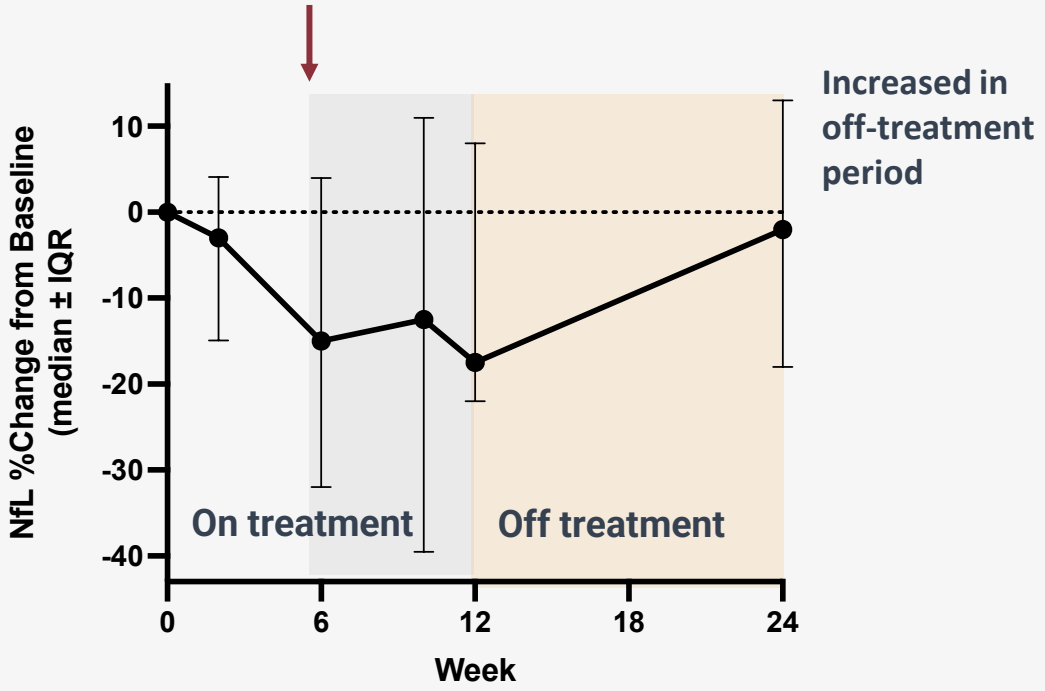
[1]Bahia El Idrissi 2016, [2]Henkel et al 2004, Kawamata et al 1992, Sta et al 2011, Kjaldgaard 2018; [3]Lee, et al. 2018; [4]Data on file

ANNEXON biosciences

ANX005 Preliminary ALS Phase 2a 12-Week Data Show Disease Progression Slowed During Treatment, Increased Off-treatment

Reduction in Plasma NfL

Reduction trend in plasma NfL during treatment period

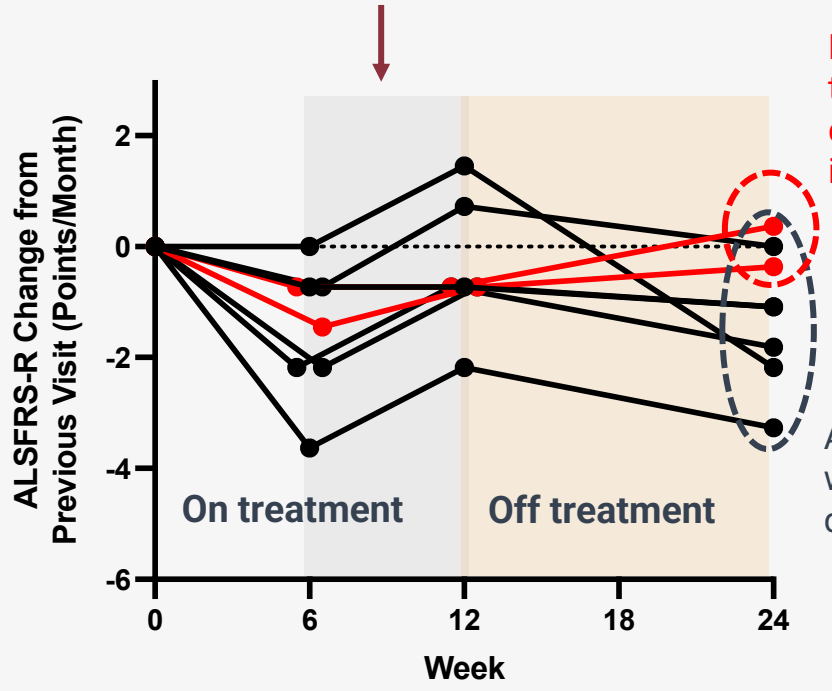


Increased in off-treatment period

On-treatment: N=8; Off-treatment: n=6 (all patients who completed 12-week treatment protocol): Data as of 12/6/2022

Impact on ALSFRS Rate of Progression

All patients showed improvement or maintenance of progression rate during treatment



Both patients that stayed on drug continued to improve

All patients who went off treatment declined

Individual patients 12 wks on drug, 12 wks off

Individual patients 24 weeks on drug

N=8 (All patients who completed 12 or 24-week treatment protocol): Data as of 12/6/2022

ANNEXON biosciences

ANX005 in Two Types of Autoimmune Hemolytic Anemia

ANNX Approach

Confirm efficacy in CAD (n=3) with prior validation in anti-complement therapy

Inform patient enrichment strategy in primary wAIHA via natural history / feeder study (n=60)

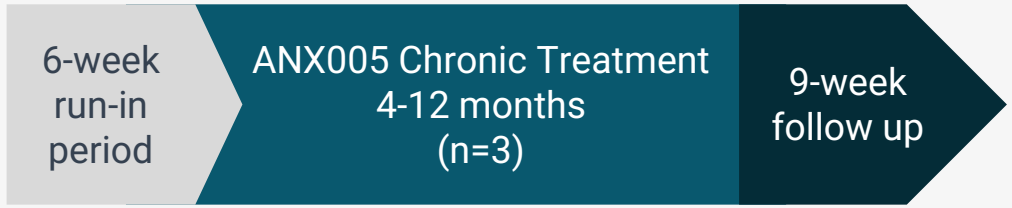
Test precision medicine approach in wAIHA in subset of patients with CAD-like complement activity (n=6)

Endpoints:

- Safety, target engagement and complement inhibition
- Anemia and hemolysis markers (e.g., hemoglobin and bilirubin)
- Quality of Life (FACIT fatigue score)

Cold Agglutinin Disease (CAD)

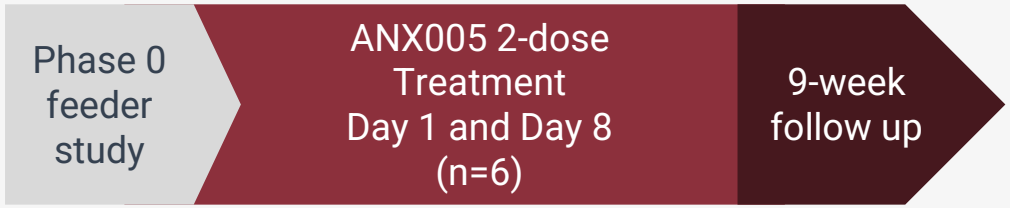
Ph2a Study Design (Confirmatory 1-Year Study)



Primary CAD patients with active hemolysis & anemia (Hgb <10 g/dL)

Warm Autoimmune Hemolytic Anemia (wAIHA)

AIHA Ph2a Study Design (Signal Finding 1-Month Study)



Primary wAIHA patients with high levels of complement activation and with active hemolysis & anemia (Hgb < 10 g/dL)

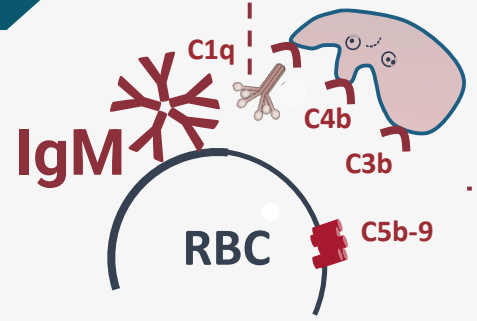
ANNEXON biosciences

Summary of AIHA Phase 2a Results

- **ANX005 generally well tolerated for up to 1 year in CAD**, longest treatment duration of ANX005 to date
- **ANX005 achieved full target engagement**, completely inhibiting C1q and downstream complement components – consistent with ANX005 in other indications
- **Positive outcomes in all CAD patients** (n=3), consistent with other complement-based inhibitors
- **Mixed outcomes in signal-finding study with wAIHA patients** (n=6)
  - Successfully identified patients with active complement deposition – blocked by anti-C1q
  - Indication that 2 doses of drug was insufficient (3-6 weeks complement inhibition)
- Due to disease heterogeneity / mixed response **will not pursue further development of ANX005 in wAIHA**

CAD and wAIHA: Autoantibody-Mediated Diseases
Different Overlapping Processes of Red Blood Cell Elimination

CAD – IgM autoantibodies
Driven by 1 process of elimination

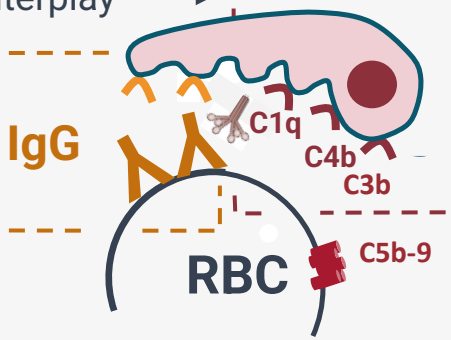


1 **Complement-receptor** dependent extravascular RBC removal by macrophages and intravascular lysis

wAIHA – IgG autoantibodies
Heterogeneous - driven by 2 processes of elimination

Complex interplay

2 **Fc Receptor-**dependent removal by macrophages



1 **Complement-receptor** dependent extravascular removal of RBC by macrophages and intravascular lysis

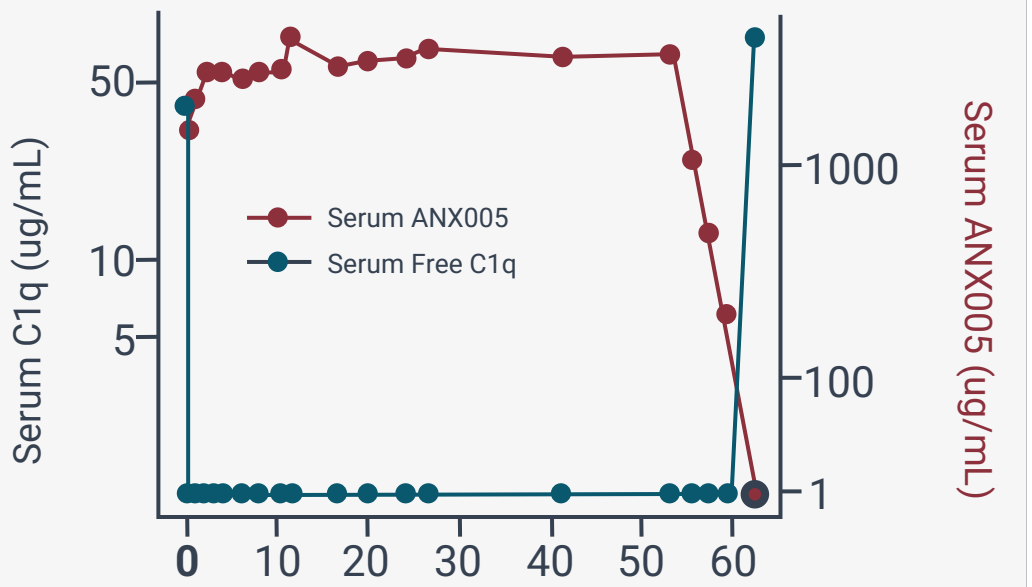
Michalak, et al., 2020 Immunity & Aging 17:3; Barcellini and Fattizzo, 2021 Blood 136:1283

ANNEXON biosciences

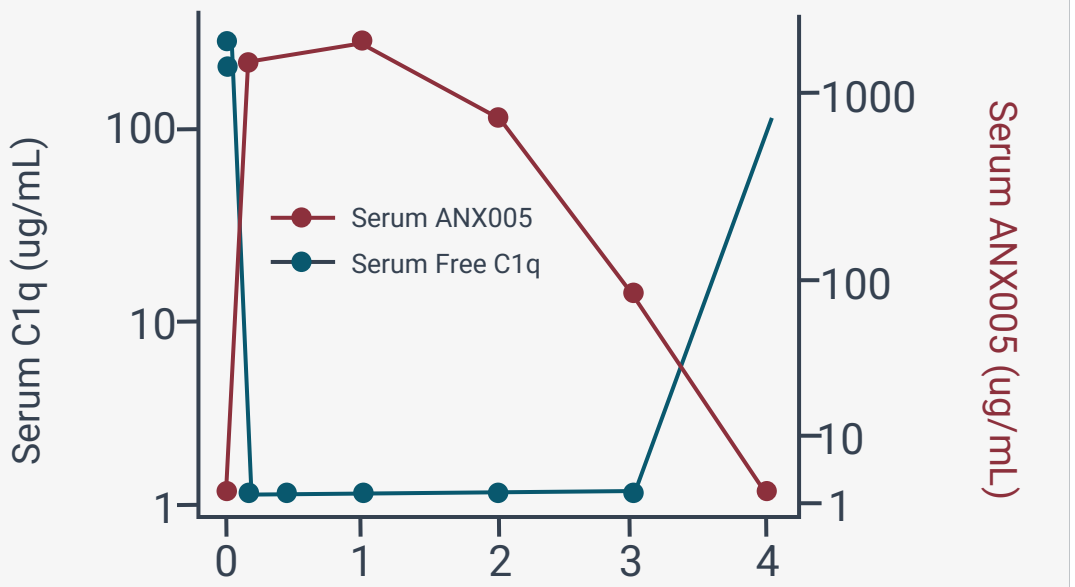
ANX005: Full Target Engagement in CAD and wAIHA Patients

Results consistent with findings in other ANX005 studies

CAD Patient 1



wAIHA Patient 1



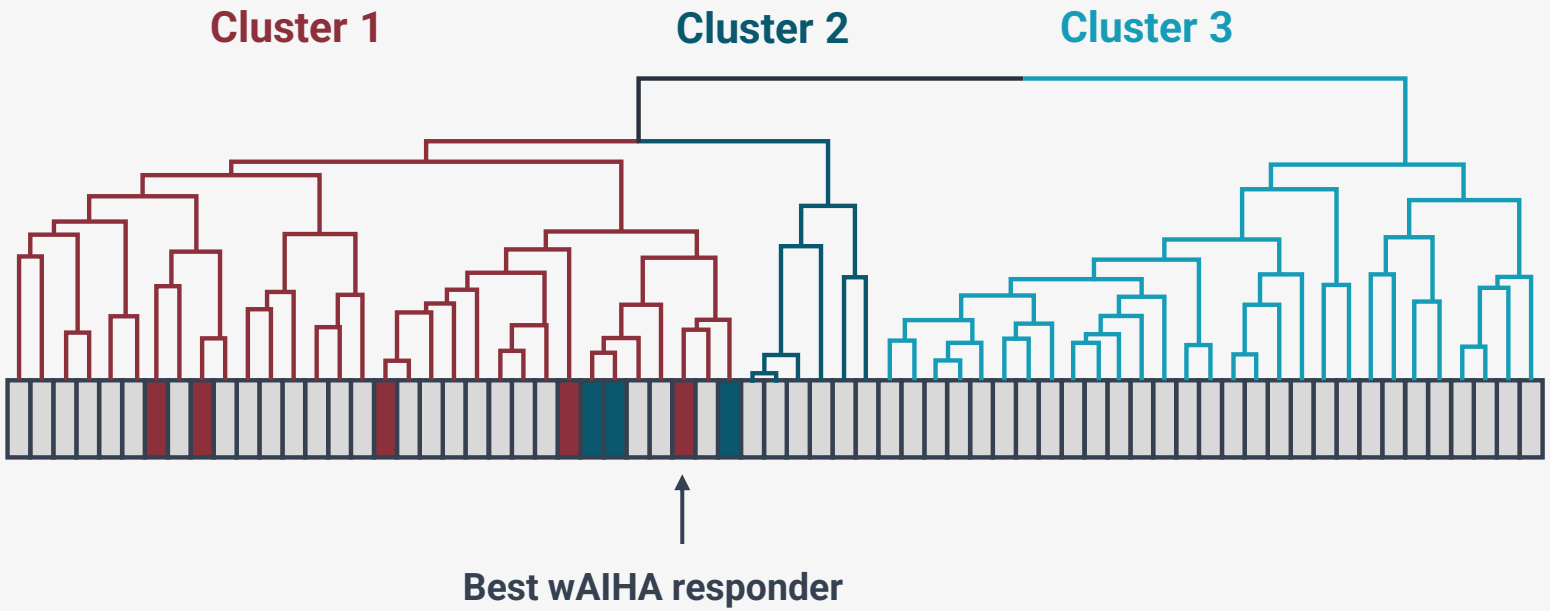
Annexon data on file

ANNEXON biosciences

Considerable Heterogeneity in wAIHA Patients
Muti-Parameter Analysis of Plasma Samples in wAIHA & CAD Patients

Cluster analysis of 17 parameters of disease pathology, including:

- Hemolysis markers (e.g., bilirubin)
- Anemia markers (e.g., hemoglobin)
- Complement levels (e.g., C3, C4)
- Complement deposition on RBC (e.g., C1q, C4d, C3d)



Key takeaways (63 samples from 60 primary wAIHA and 3 CAD patients)

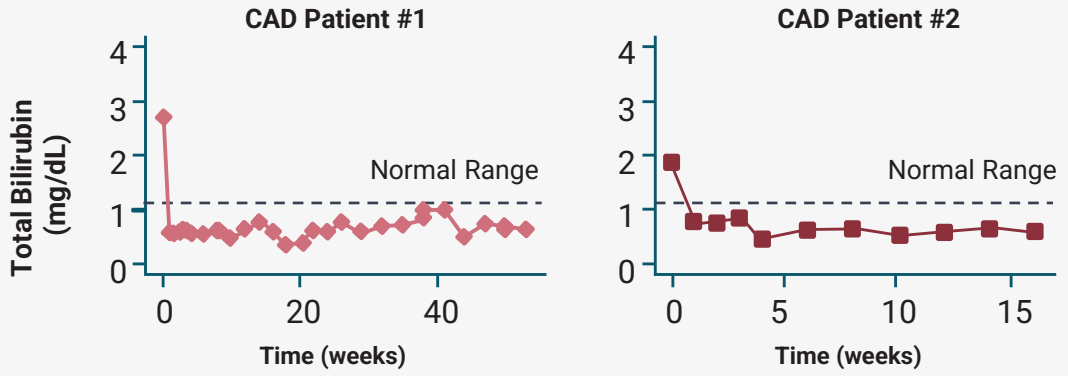
- Samples from 60 patients with primary wAIHA revealed significant heterogeneity within multiple subgroups
- Samples from three CAD patients clustered together (all with with low C4 levels, <1.5 lower limit of normal)
- Samples from five wAIHA patients with low, CAD-like levels of C4 selected for treatment (N=5) demonstrated significant heterogeneity in multiple baseline parameters; best responder most closely resembled CAD based on all parameters

Annexon data on file

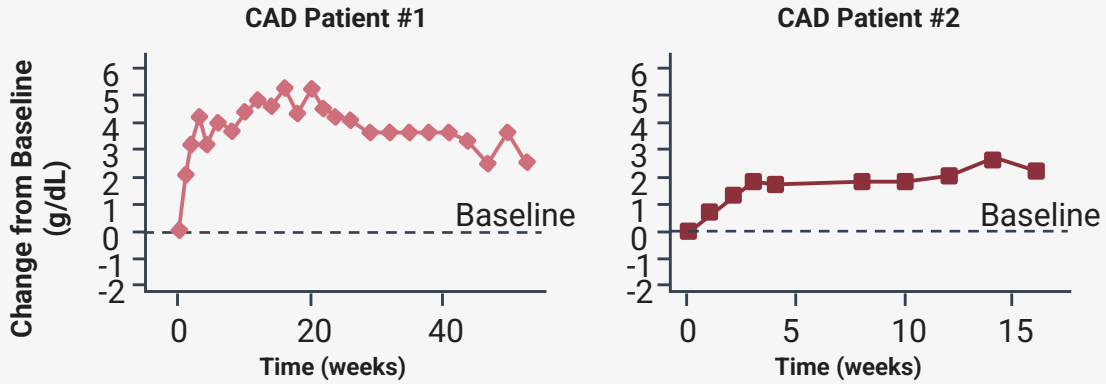
ANNEXON biosciences

ANX005 in CAD: Rapid Inhibition of Hemolysis and Sustained Increases in Hemoglobin

Total Bilirubin



Hemoglobin Change From Baseline



CAD: Key Data Takeaways

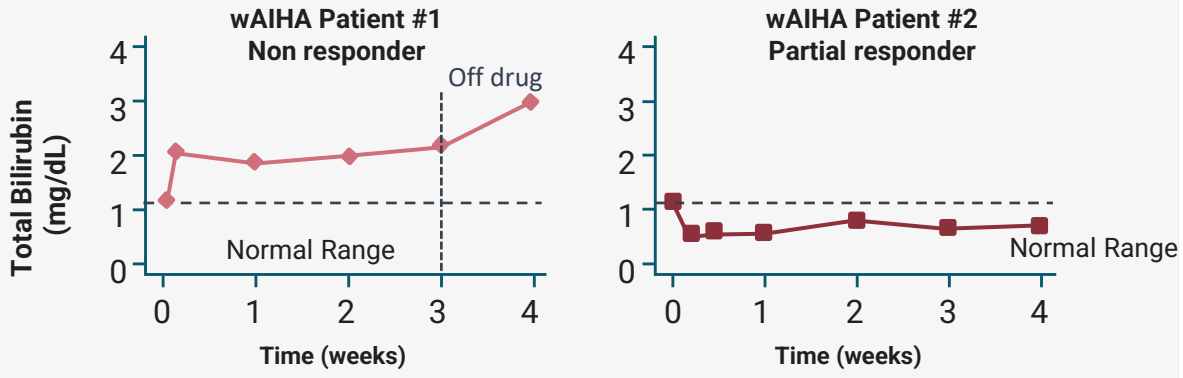
- **ANX005 fully blocked complement deposition on red blood cells in all patients**
- **Rapid and sustained normalization of hemolysis (bilirubin)**
- **Significant and durable improvement in anemia (increase in hemoglobin)**
  - Hgb ≥2 g/dL & achieved Hgb > 10 g/dL
- **ANX005 generally well tolerated for up to 1 year**
  - Longest treatment duration of ANX005 to date

Annexon data on file

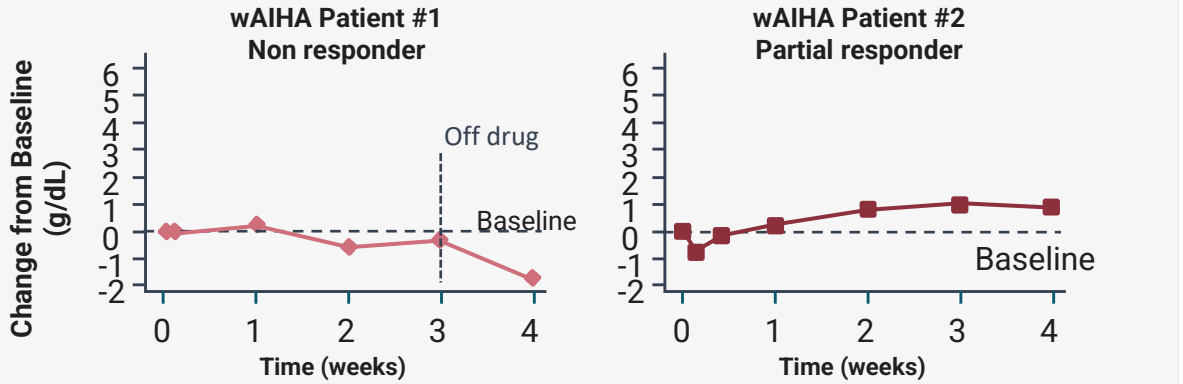
ANNEXON biosciences

ANX005 in wAIHA: Complement Deposition Blocked on RBC, But Mixed Effects on Hemolysis and Hemoglobin

Total Bilirubin



Hemoglobin Change From Baseline



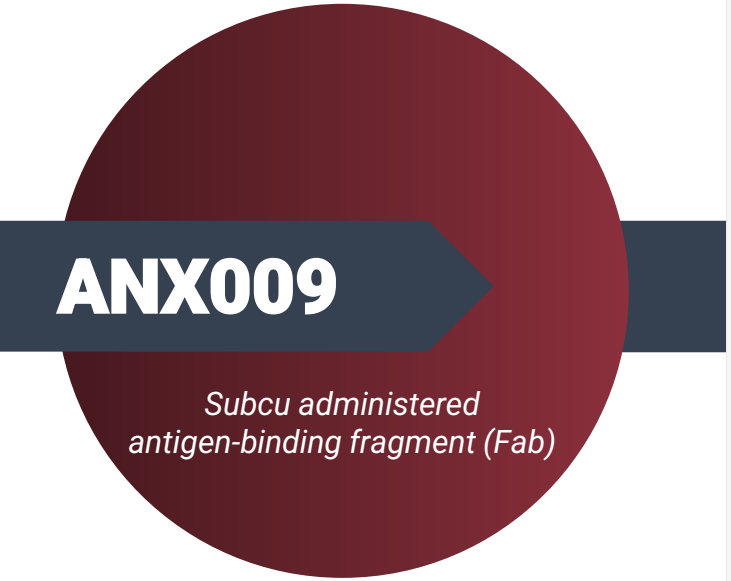
wAIHA: Key Data Takeaways

- **ANX005 fully blocked complement deposition on red blood cells in all patients**
  - Measured by flow cytometry (data not shown)
- **Mixed responses on bilirubin and hemoglobin**
- ANX005 generally well tolerated

Annexon data on file

ANNEXON biosciences

ANX009 Selectively Inhibits Complement Activation in Vascular Space



Key Attributes

- ✓ **Subcutaneous formulation** of an antigen-binding fragment (Fab)
- ✓ **Target Engagement:** Selectively inhibits C1q *in the vascular space*
- ✓ **Safety:** Well-tolerated in Phase 1 trial, twice weekly dosing provided sustained C1q inhibition in the circulation
- ✓ **Dosing:** Designed to **enable chronic dosing** for use in future trials of autoimmune indications

ANNEXON biosciences

Potential First-In-Class Approach for Lupus Nephritis; Data Expected 1H23

Endogenous, pathogenic autoantibodies against C1q enhance its activity and uniquely amplify kidney inflammation and damage

LN Overview

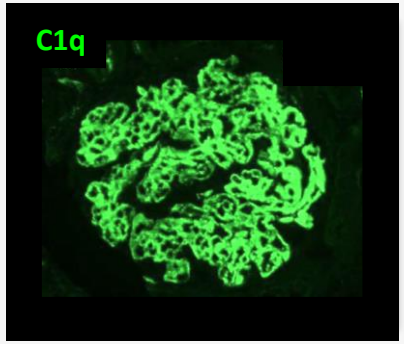
~60,000 US patients/year

Pathogenetic auto-antibodies against C1q (PACAs) enhance LN disease activity

Role of C1q

C1q and PACAs amplify kidney inflammation and damage

ANX009 blocks binding, activation & **tissue damaging inflammation in LN**



C1q targeting the renal glomerulus

ANX009

Targeting patients with high baseline complement activity by increased C4d/C4

Well-tolerated in Phase 1 trial, twice weekly dosing provided sustained C1q inhibition in the circulation

Phase 1b signal-finding trial underway, with initial data expected in 1H23

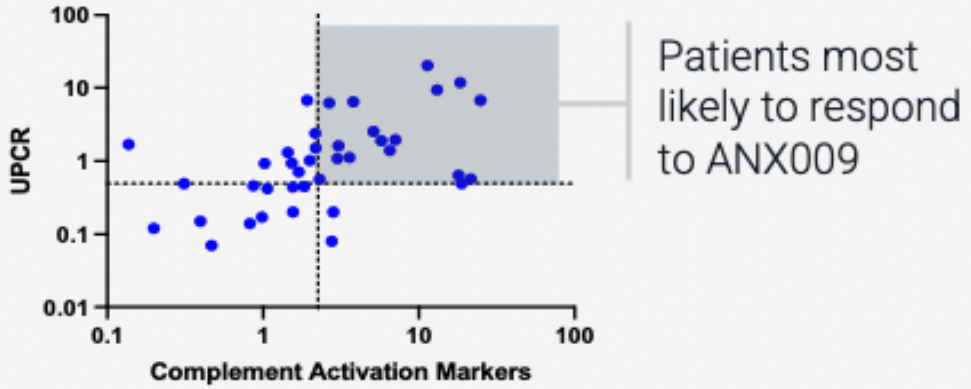
*Induced by injection of auto-reactive antibodies against kidney glomerular basement membrane antigens
Trouw et al. J Clinical Investigation (2004) 114:679

ANNEXON biosciences

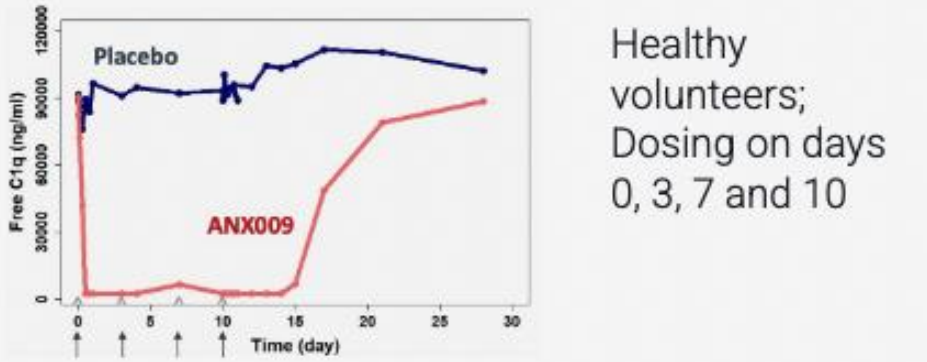
Preclinical and Phase 1 Support for ANX009 in Lupus Nephritis

Precision Medicine Approach

High baseline complement activity correlated with disease activity



Full inhibition of C1q in serum with ANX009 in Phase 1 study



Selectively Inhibiting C1q to Stop Complement-Mediated Disease

Annexon data on file

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ANX105 Next Generation Inhibitor of C1q & Classical Pathway

Key Attributes

- ✓ **Full-length mAb for IV administration**
- ✓ **Target Engagement:** Designed to fully inhibit C1q in blood and CSF
- ✓ **Dosing:** Designed with potentially improved dosing properties for use in future trials of autoimmune and neurodegenerative indications
- ✓ **Phase 1 SAD study in normal healthy volunteers ongoing**

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A Mission to Enable People to Live Freely from Complement-mediated Diseases

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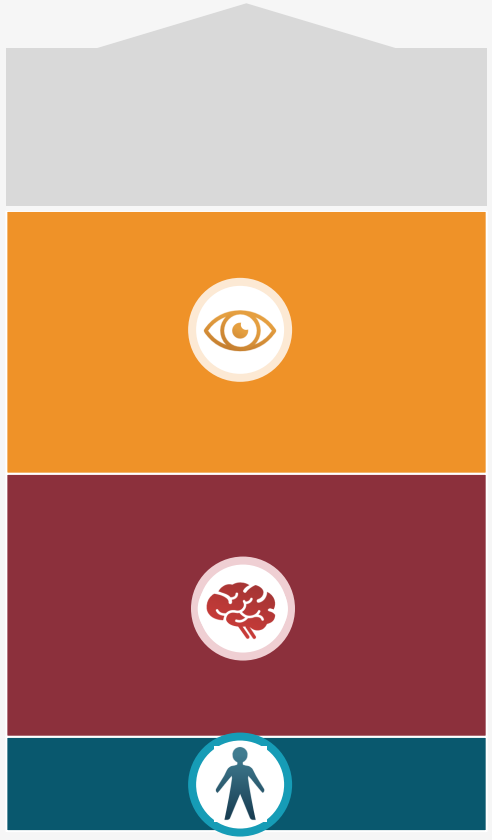
Game-Changing Opportunity for C1q-directed Complement Therapies in Current Indications and Beyond

Significant Unmet Need

- **0** **C1q-directed complement agents** on the market or in late-stage development
- **0** **Disease-modifying treatments** available for GBS or HD
- **0** Treatments that target **both up and downstream** complement pathway for GA
- **0** **Orally administered, small molecule** complement treatments available

Multi-Billion Market Opportunity



Expansion into additional complement-mediated diseases of the body, brain and eye

>$10 BILLION

Market opportunity in current pipeline indications*

*Based on market data and company estimates

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2023 Clinical Milestones Primed to Unlock Significant Value

Well capitalized with runway into 2025

Complete enrollment in pivotal GBS trial	**ANX005** Phase 3 complete enrollment expected in 2H 2023
Initiate pivotal HD trial	**ANX005** Phase 2/3 initiation expected in 2023
Demonstrate clinical efficacy in GA	**ANX007** Phase 2 data expected in mid-2023
Initiate clinical POC trial with oral, small molecule	**ANX1502** Phase 1 MAD data in healthy subjects expected by end of 2023 POC trial initiation in CAD patients expected by end of 2023
Demonstrate efficacy signal in “next wave” indications and target engagement with next generation mAb	**ANX005** Ph 2 ALS data expected in 2023 **ANX009** Ph 1 LN data expected in 1H 2023 **ANX105** Ph1 data expected in 2023

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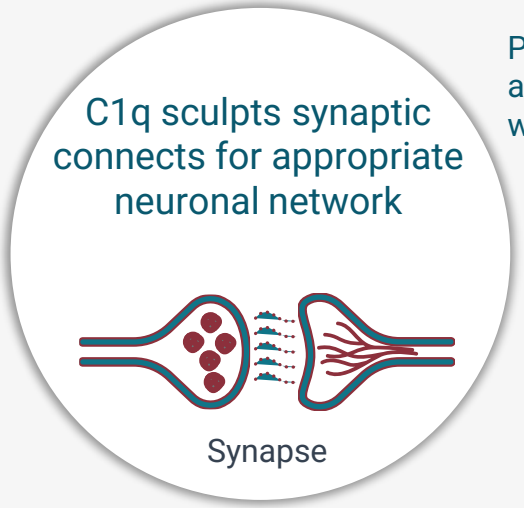
APPENDIX

Loss of Functioning Synapses Results in Neurodegeneration

Blocking C1q protects functioning synapses, prevents loss and decreases disability[2]

C1q's Normal Role In Development

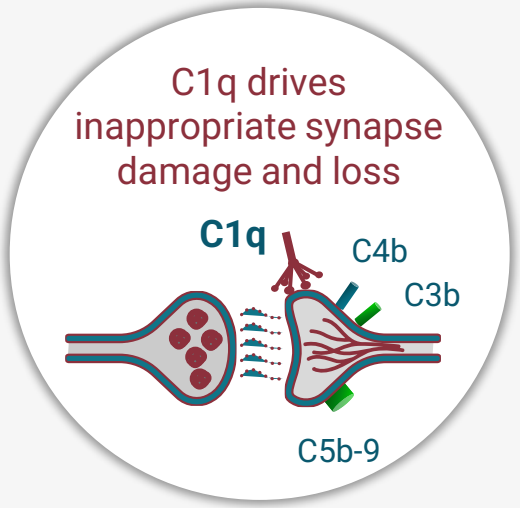
- C1q recognizes, tags & drives removal of excess synapses
- Strong synapses remain to form appropriate circuits and normal brain health



Pathway turns off after developmental window

C1q's Role In Neurodegenerative Disease

- C1q recognizes, tags & drives removal of functioning synapses
- Triggers inappropriate synapse damage and loss, neuroinflammation and degeneration



Chronic pathway activation and functional decline

[1]Wilton 2021 doi.org/10.1101/2021.12.03.471180; Hong 2016 *Science* 10.1126/science.aad8373; Stevens 2007 *Cell* DOI 10.1016/j.cell.2007.10.036; Fonseca, 2004, *J Neurosci*; Dejanovic, 2018, *Neuron*; Vukojicic, 2019, *Cell Reports*; Howell, 2011, *J Clin Inves*; Williams, 2016, *Mol Neurodegen*; Jiao, 2018, *Mol Neurodeg*; Lui, 2016, Cell **165**:921; Krukowski, 2018, Int.*J Mol Sci*; Holden, 2021, *Science*; Annexon NfL reduction in SOD1 model, unpublished; Absinta, *Nature*, 2021

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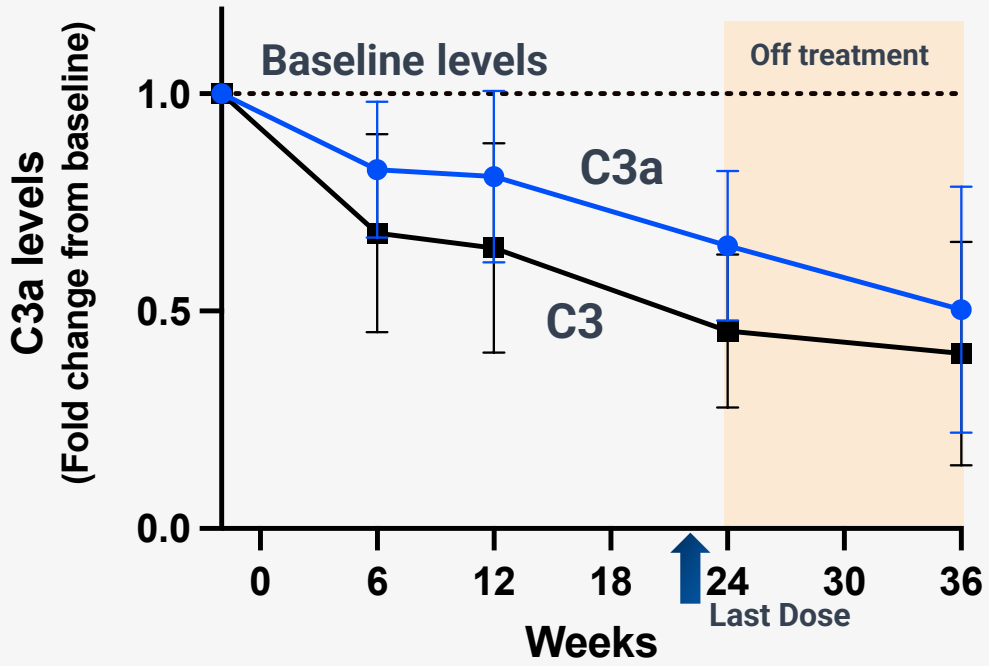
Evidence of Reduced Downstream Complement Activation & Neuroinflammation Through Entire 9 Month Study

Drug Effects Continue into Off-treatment Period



N = 23

ANX005 showed:

- Reduction of downstream complement activation (C3a)
- Reduction of neuroinflammation (C3)
  - C3 is produced by activated, neurotoxic astrocytes in the brain[1]

[1]Liddelow, Barres, 2017 *Nature* **541**: 481–487

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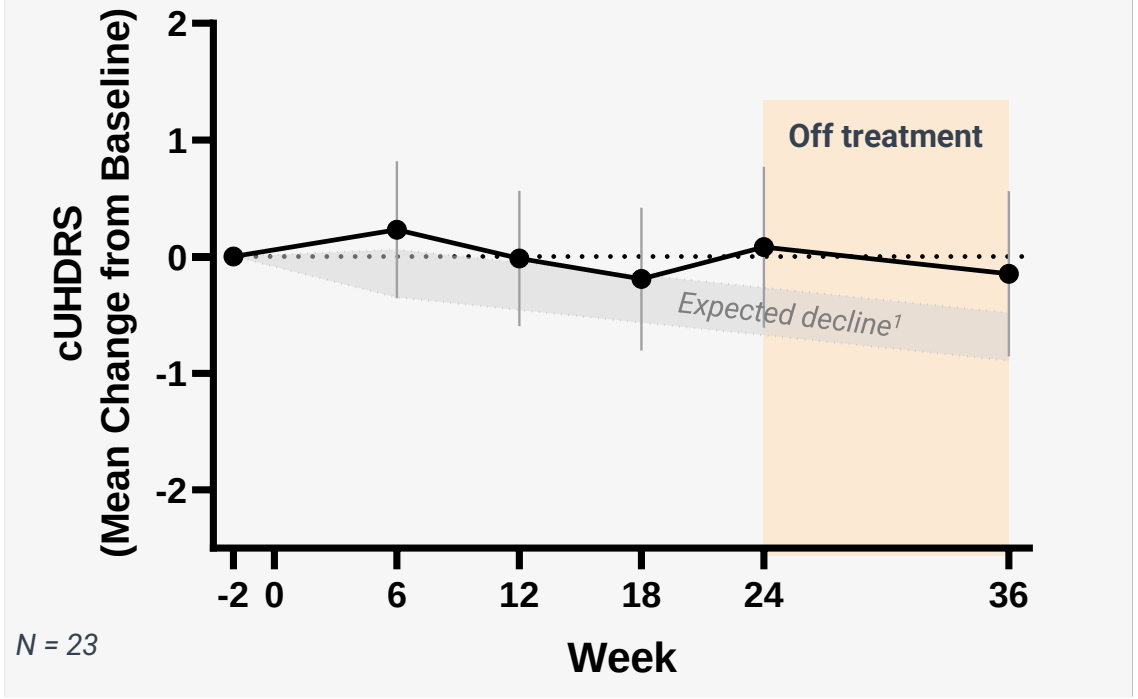
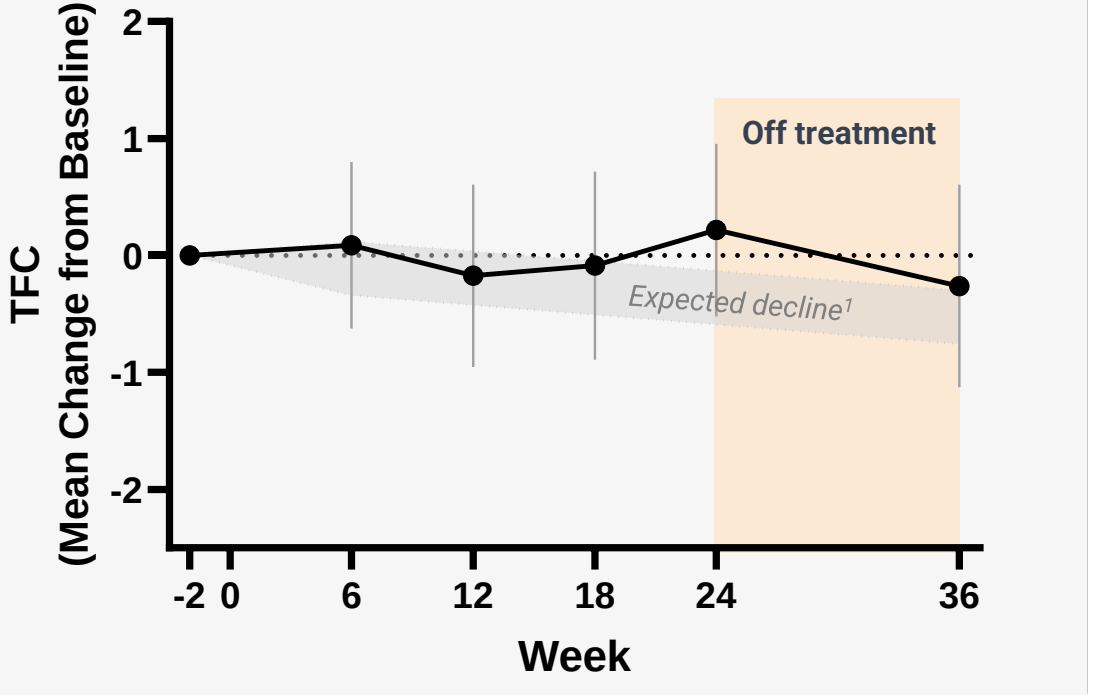
Clinical Disease Progression Stable in Overall Patient Population Through Entire 9-month Study

cUHDRS Stable Over 9 Months



N = 23

TFC Stable Over 9 Months



MMRM; LS means +/- 95% CI

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

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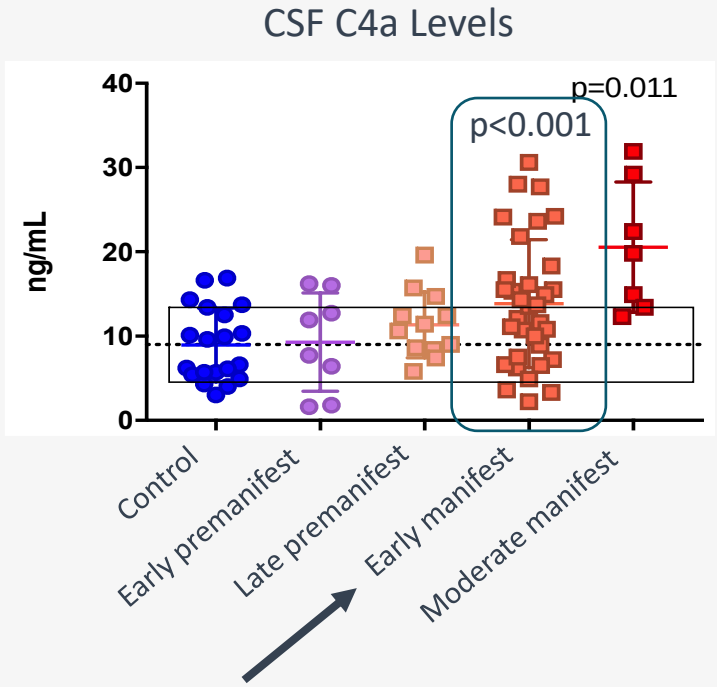
Complement Activation Correlates with Disease and Functional Decline in HD

Patients with higher baseline complement activity may be more likely to respond to anti-C1q therapy

CSF C4a Elevated and Increase with HD Progression*



Early manifest consistent with patients enrolled in current study

CSF C4a Activation Correlate with HD Functional Decline

Clinical endpoints	p-value	
Total functional score (TFC)	0.0333	Motor & Function
Total motor score (TMS)	0.0181	
Disease burden score (DBS)	0.1310	
Symbol digit mod. Test (SDMT)	0.0324	Cognitive Scales
Verbal fluency	0.0255	
Stroop color naming (SCN)	0.0454	
Stroop word recall (SWR)	0.0710	

*Higher complement activity in CSF (C4a) of HD Patients associated with disease severity & functional decline
Presented at HSG, November 2021; Annexon Collaboration with Ed Wild UCL

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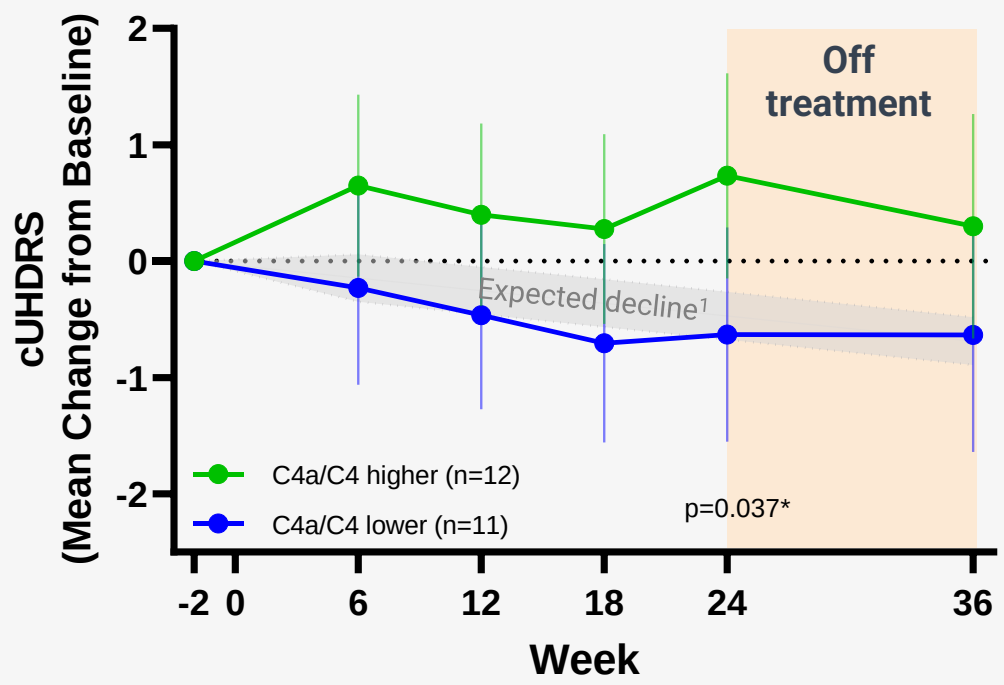
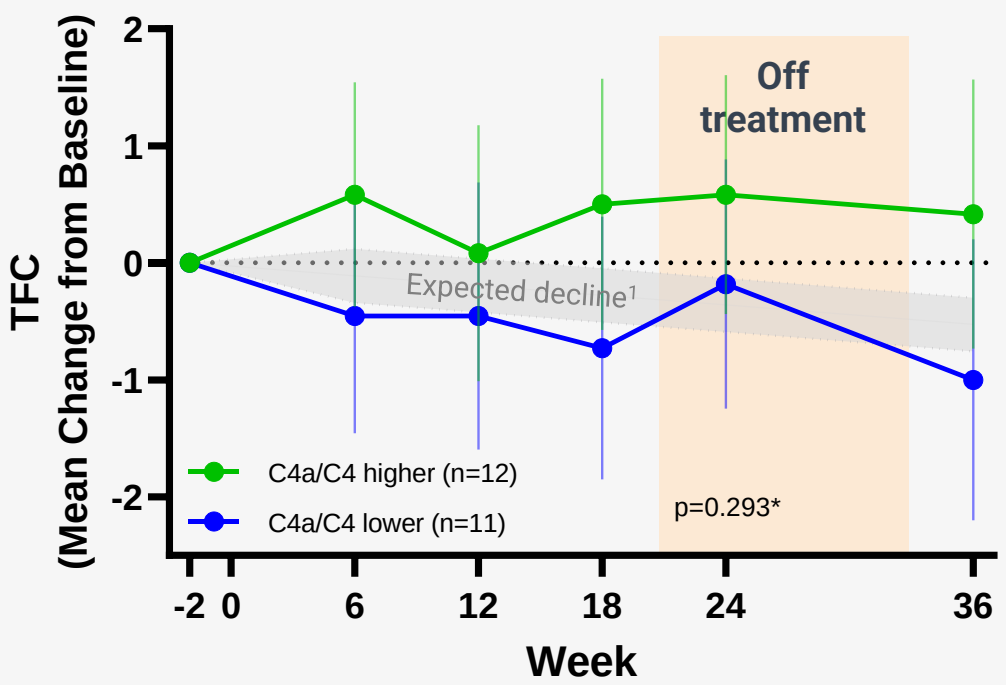
Rapid Benefit Maintained in Patients with High Baseline Complement Activity Through Treatment and Follow-up Periods

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

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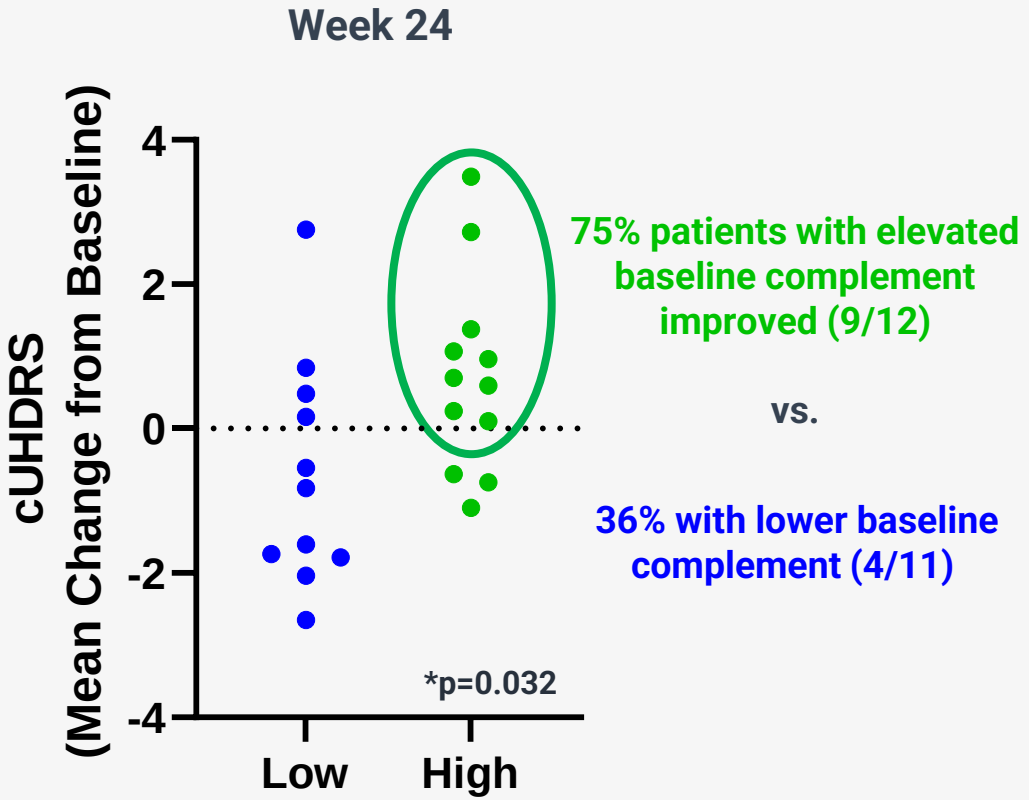
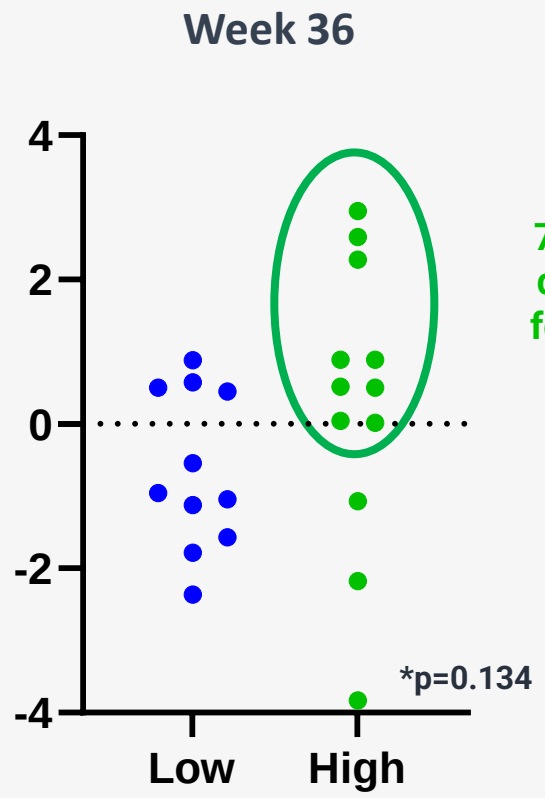
75% of Patients with High Baseline Complement Levels Showed Improvement at Week 24, Maintained at Week 36r

Twice as many patients with high complement improved compared to patients with low complement

Week 24 cUHDRS (Change from Baseline)



Week 36 cUHDRS (Change from Baseline)



Baseline Complement Activity (C4a/C4)

Baseline demographics evenly matched between patients with higher and lower CSF complement activation
*Wilcoxon-Mann-Whitney Test

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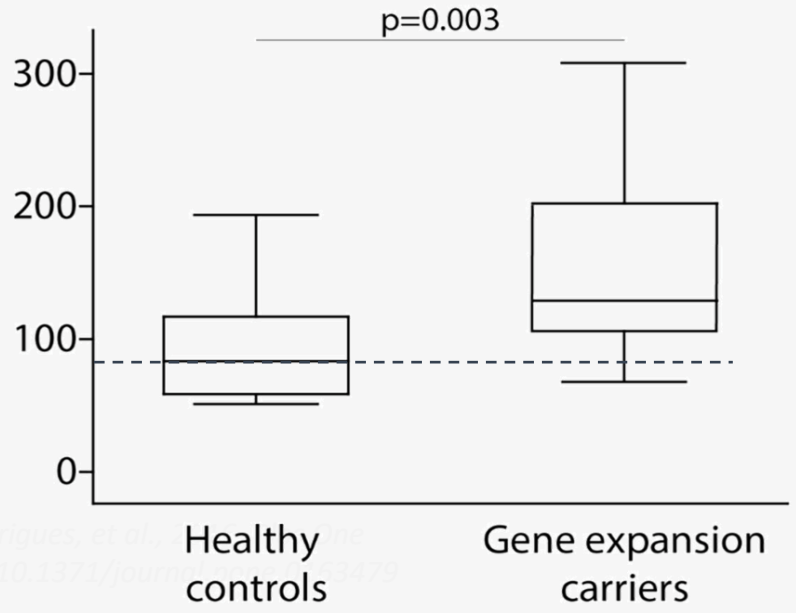
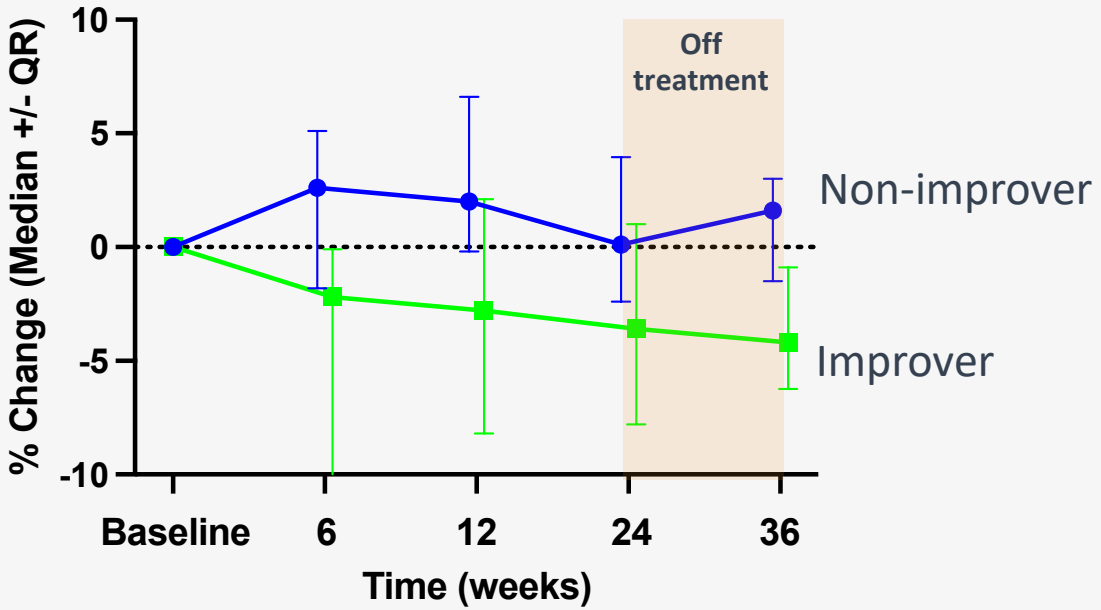
Independent Marker of Inflammation in HD (YKL-40*) Decreased in ANX005-treated Patients Exhibiting Clinical Improvement

YKL-40 Increased in CSF of HD Patients



Rodrigues 2016 *PLoS One* **11** e0163479

ANX005-treated Improvers Showed Rapid, Consistent Decrease of YKL-40



Annexon data on file

*Produced by activated glia - Elevated in HD and other neurological diseases

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