A Phase 2 Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous ANX005 in Patients with, or at Risk of, Manifest Huntington's Disease (HD)

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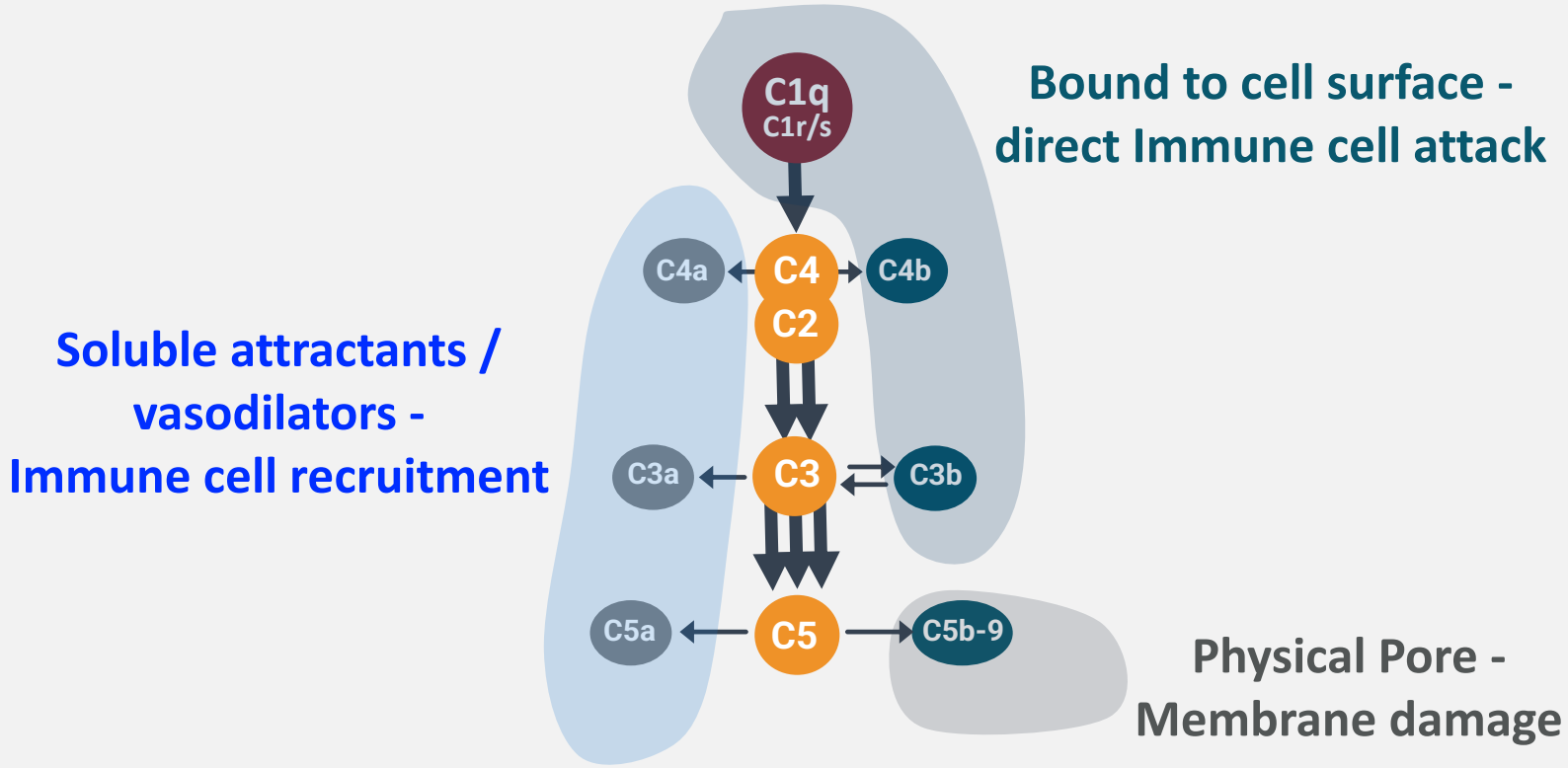
Dr. Kumar's institution has received compensation for serving as a consultant for AbbVie, Acorda Therapeutics, **Annexon Biosciences**, Cerevel Therapeutics, Roche, Supernus, and Teva Pharmaceuticals. Dr. Kumar has stock in CenExel and Research Catalyst, LLC. Dr. Kumar's institution has received research support from AbbVie, Addex Pharma, Alexza, **Annexon Biosciences**, Annovis, Biohaven, BioVie, Cerevel Therapeutics, CHDI Foundation, CND Life Sciences, Cognition Therapeutics, Eli Lilly, Enterin, Impax Laboratories, Integrative Research Laboratories, Neuraly, Neurocrine Biosciences, Neuron23, Lundbeck, Neuroderm, Pharma Two B, Praxis, Prilenia Therapeutics, PTC Therapeutics, Revance Therapeutics, Roche, Sage Therapeutics, Sanofi, Scion NeuroStim, Spark Neuro, Supernus, Takeda Pharmaceuticals, Triplet Therapeutics, Transposon Therapeutics, and Uniqure. Dr. Kumar's institution has received compensation for his serving on the Speakers Bureau for Acorda Therapeutics, Kyowa Kirin, and Teva Pharmaceuticals. Dr. Kumar has received personal compensation for serving as a Medical Director with CenExel RMCR; personal compensation for serving as a Managing Member with Research Catalyst, LLC; personal compensation for serving as an officer or member of the Board of Directors for Research Catalyst, LLC; personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Impel Pharma; and personal compensation for serving on a Speakers Bureau for Supernus.

Classical Complement Cascade is Multi-Step, Amplifying Pathway Initiated by C1q

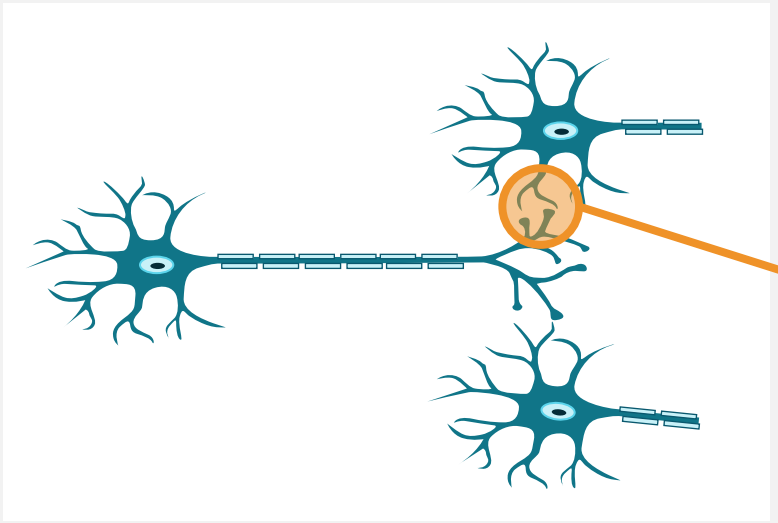
C1q activation results in series of proteolytic products that tag cells for elimination, recruit immune cells and damage cell membranes

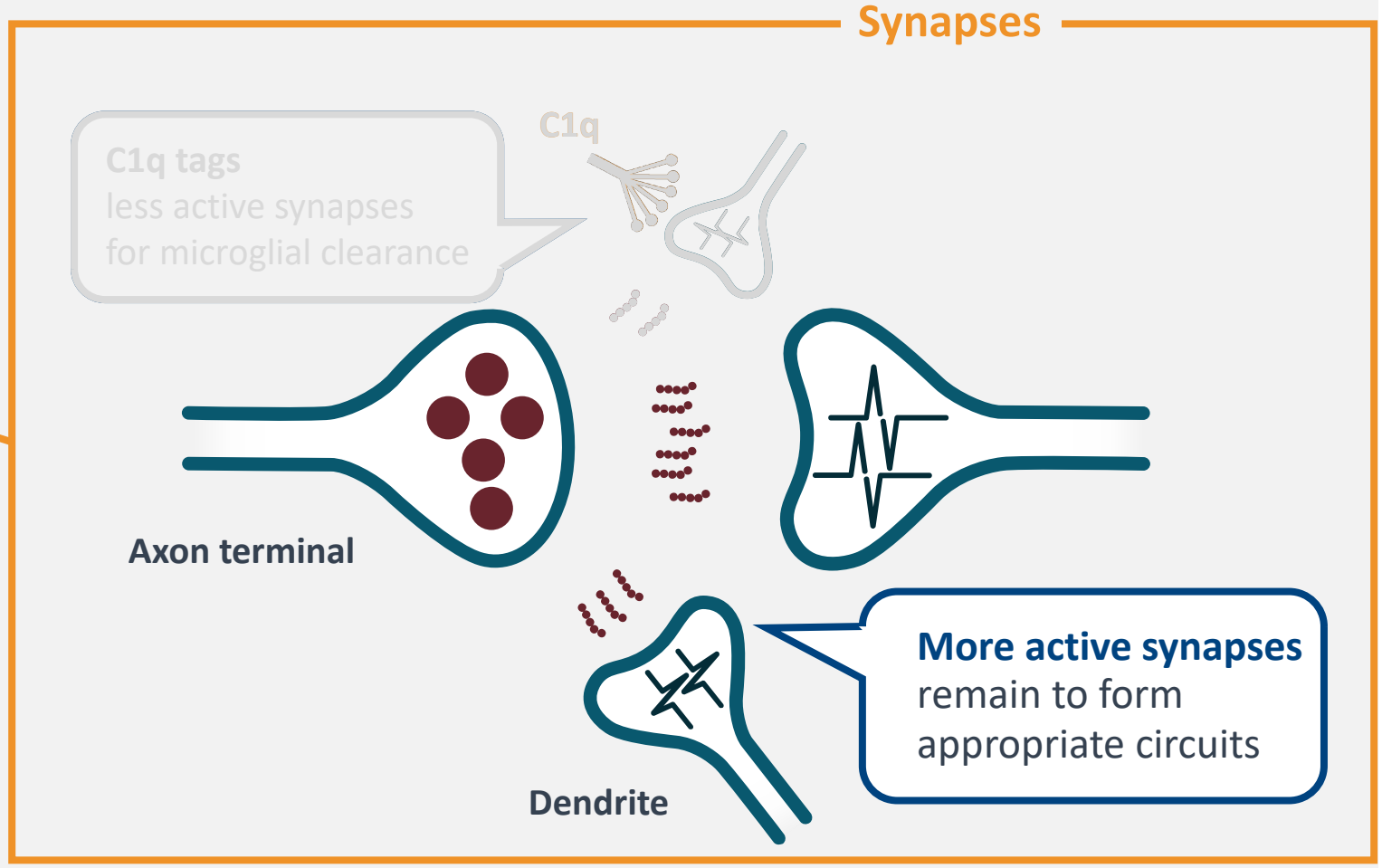


McGonigal et al. Acta Neuropathologica Communications (2016) 4:23

In Development, C1q Activates the Classical Complement Cascade to Prune Excess Synapses, Sculpting CNS Neuronal Circuitry

This process is highly regulated during normal developmental windows



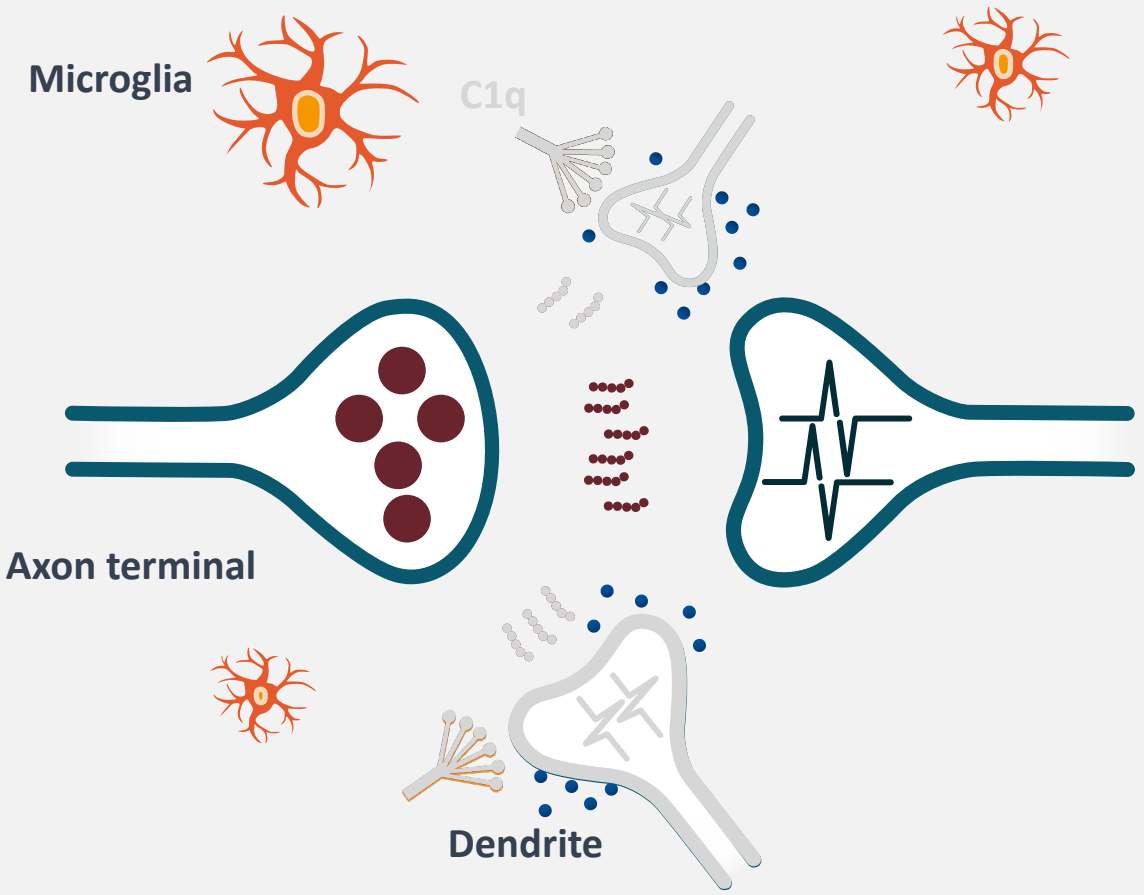


Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS, Nouri N et al. The classical complement cascade mediates CNS synapse elimination. *Cell*. 2007;131:1164-1178.
Gomez-Arboledas A, Acharya MM and Tenner AJ. The role of complement in synaptic pruning and neurodegeneration. *ImmunoTargets and Therapy*. 2021;10:373-386 .

Key Triggers in Neurodegenerative Diseases Lead to Excessive C1q Activity, Neuroinflammation and Neuronal Damage

This process is not regulated and leads to chronic, unresolving inflammation and degeneration

1. C1q binds synapses on stressed neurons and triggers complement deposition and synapse damage
2. Complement activation signals immune cells recruitment
3. Immune cells remove complement-coated synapses
4. Neurons lose synaptic input and trophic support
5. Neuronal damage and loss

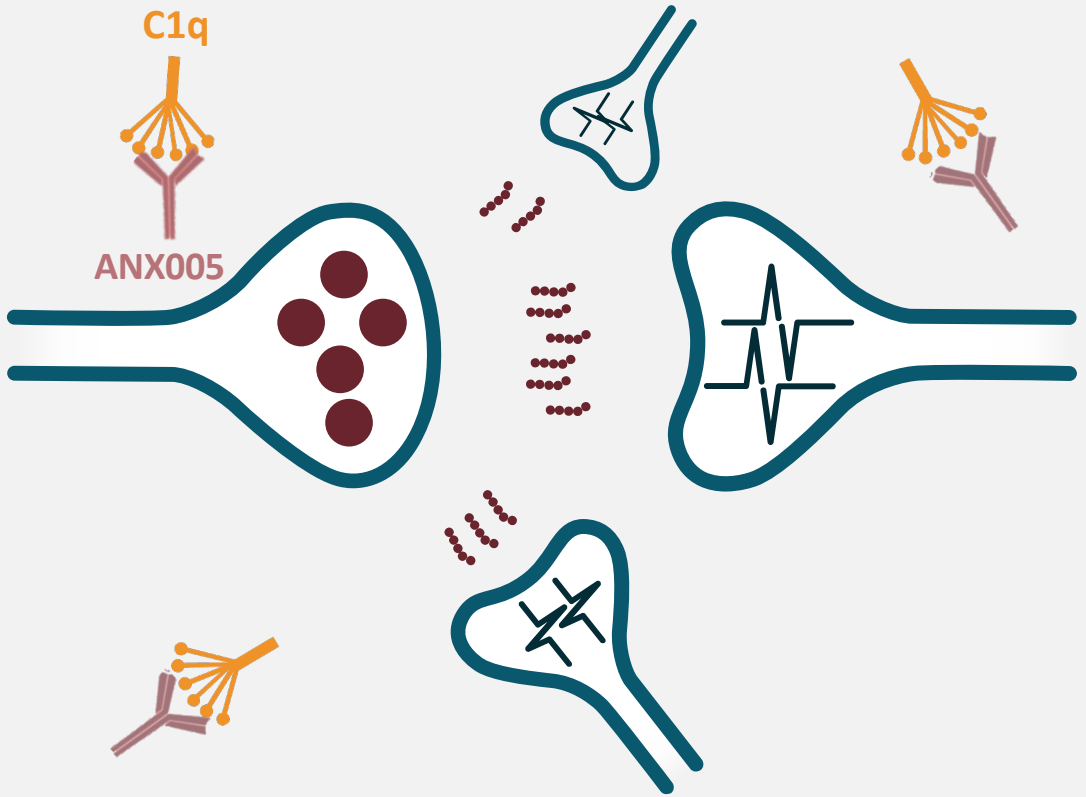


Wilton 2021 doi.org/10.1101/2021.12.03.471180; Hong 2016 Science doi 10.1126/science.aad837; Stevens 2007 Cell doi 10.1016/j.cell.2007.10.036; Fonseca, 2004, J Neurosci; Dejanovic, 2018, Neuron; Vukojicic, 2019, Cell Reports; Howell, 2011, J Clin Inves; Williams, 2016, Mol Neurodegen; Jiao, 2018, Mol Neurodeg; Lui, 2016, Cell 165:921; Krukowski, 2018, Int.JMol Sci; Holden, 2021, Science; Annexon NfL reduction in SOD1 model, unpublished; Absinta, Nature, 2021

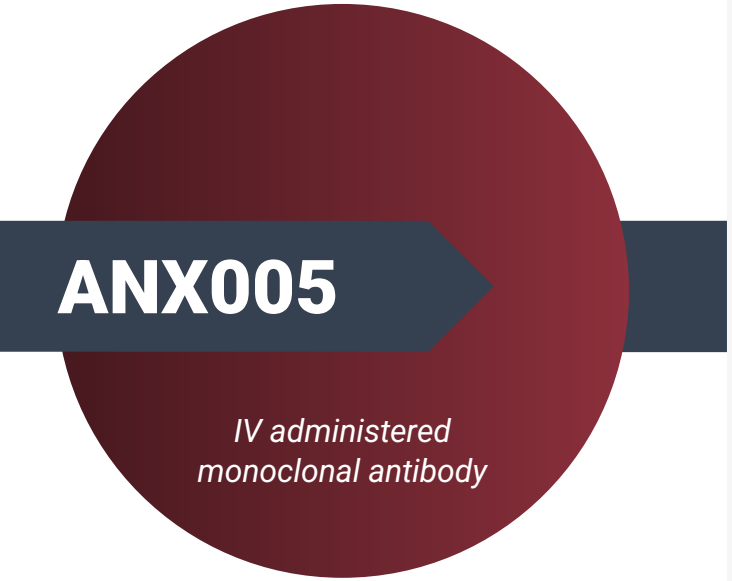
Inhibition of C1q Selectively Blocks Initiation of the Classical Cascade and May Protect Synapses and Reduce Inflammation to Slow Disease Progression

Blocking dysregulated C1q activity may protect against synapse loss and neuronal damage

Importantly,
targeting C1q blocks all downstream components of the classical pathway



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:** Completed or ongoing studies in Guillain-Barré syndrome (GBS), Huntington's disease (HD), cold agglutinin disease (CAD) & amyotrophic lateral sclerosis (ALS)

Administered to >200 patients to date

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

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

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

Study Population

- Adults (*mHTT+)* with manifest HD ("Early HD")
- Total CAP score >400
- UHDRS independence score ≥80%

Primary Endpoints

- Safety and tolerability of ANX005
- PK of ANX005 in serum & cerebrospinal fluid (CSF)
- PD as measured by C1q, C4a, and NfL levels in blood and CSF

Exploratory Endpoints

- Composite Unified Huntington's Disease Rating Scale (cUHDRS)

ANX005 Phase 2 Trial Patient Baseline Demographics

Study Participant Characteristics	All Patients (N=28)	Treatment Completers (n=23)	TRACK-HD* (N=123)	ENROLL-HD* (N=1071)
Age, mean (SD), years	49.7 (12.5)	48.5 (13.3)	48.8 (9.8)	49.3 (13.6)
Female, %	43	35	45	55
CAG repeat length, mean (SD)	44.6 (3.5)	45.1 (3.7)	43.7 (3.0)	43.5 (3.5)
CAP score, mean (SD)	505.7 (57.9)	512.2 (60.4)	NR	NR
Manifest HD, n (%)	25 (89.3)	21 (91.3)	123 (100)	739 (69%)
cUHDRS, mean (SD)	10.4 (3.2)	10.1 (2.9)	11.7 (2.9)	NR
Total Functional Capacity, mean (SD)	10.6 (2.2)	10.4 (2.3)	10.9 (2.0)	9.5 (3.6)
Total Motor Score, mean (SD)	21.6 (12.6)	22.3 (11.4)	23.7 (10.8)	26.9 (22.3)
Symbol Digit Modalities Test, mean (SD)	29.7 (11.3)	28.8 (11.0)	33.6 (10.2)	32.4 (17.5)
Stroop Word Reading Test, mean (SD)	59.0 (18.7)	56.7 (16.7)	78.3 (19.5)	67.6 (28)

- ~90% of patients were “early manifest HD”
- Demographics consistent with prior HD natural history study cohorts (ie, TRACK-HD* and ENROLL-HD*)

* TRACK-HD and ENROLL-HD, HD natural history studies. For illustrative purposes only—differences exist between patient demographics, study designs, and other factors, and caution should be exercised when comparing data across studies.
NR=not reported

Chronic Dosing of ANX005 Generally Well-Tolerated with Favorable Benefit-Risk Profile Demonstrated in HD

Treatment-Emergent Adverse Events	Safety Population (N=28)	
	All Grades, n (%)	Grade 3, n (%)
Any reported TEAEs	28 (100.0)	12 (42.9)
Most Common TEAE		
Infusion Related Reactions (IRR)	28 (100.0)	8 (28.6)

- No deaths and no serious infections observed
- IRR primarily first dose effect — none after 2nd dose
- Stable NfL levels in CSF

No grade 4 TEAEs reported.

Chronic Dosing of ANX005 Generally Well-Tolerated with Favorable Benefit-Risk Profile Demonstrated in HD

Treatment-Emergent Adverse Events	Safety Population (N=28)	
	All Grades, n (%)	Grade 3, n (%)
Most Common TEAEs (non-IRR)	25 (89)	6 (21)
Dizziness	5 (18)	0 (0)
Nausea	5 (18)	0 (0)
Headache	4 (14)	0 (0)
Vomiting	4 (14)	0 (0)
COVID-19	4 (14)	0 (0)
Rash	4 (14)	1 (4)

- Two treatment discontinuations unrelated to drug (COVID-19, consent withdrawn)

No grade 4 TEAEs reported.

Chronic Dosing of ANX005 Generally Well-Tolerated with Favorable Benefit-Risk Profile Demonstrated in HD

Treatment-Emergent Adverse Events	Safety Population (N=28)	
	All Grades, n (%)	Grade 3, n (%)
Serious TEAEs	2 (7)	2 (7)
Related to ANX005	2 (7)	2 (7)
Infections	0 (0)	0 (0)
TEAE with Fatal Outcome	0 (0)	0 (0)

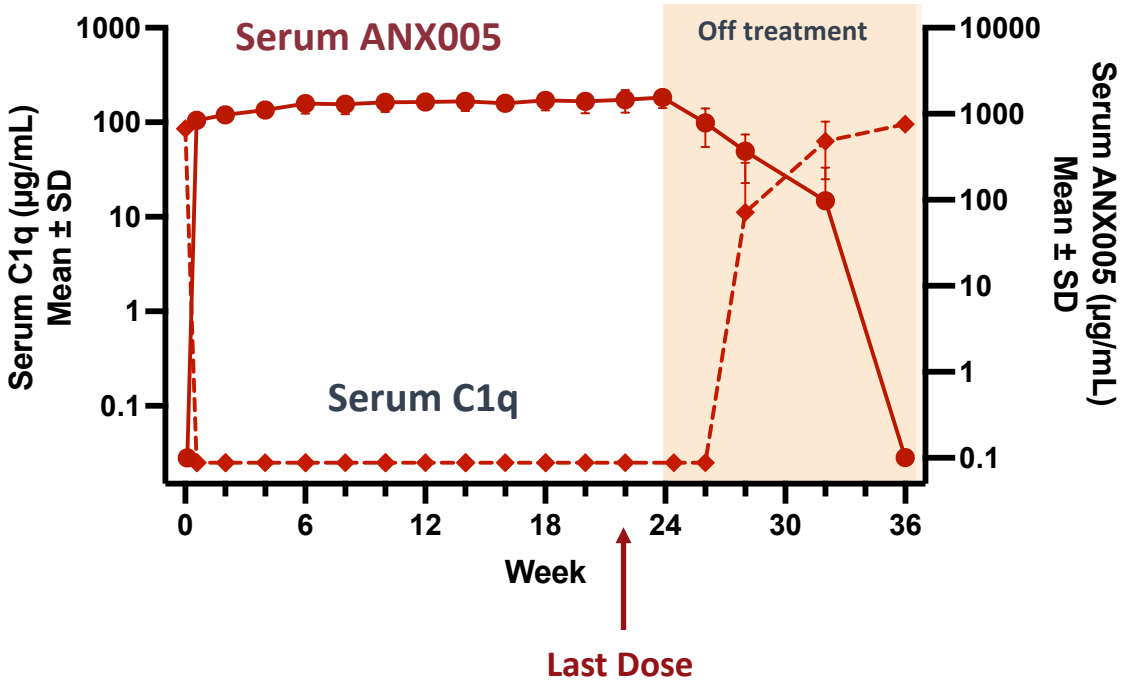
- Three treatment discontinuations potentially related to drug: all improved/resolved after drug cessation
  - One event each: idiopathic pneumonitis (SAE), systemic lupus erythematosus (SAE), asymptomatic hemolytic anemia (AE)
- All cases of treatment discontinuation had elevated ANA titers at baseline; no patients with normal ANA titers developed SAE
- Enhanced screening of ANA autoantibody levels at baseline and additional monitoring incorporated into ongoing/future trial to reduce risk in chronic ANX005 dosing protocols

No grade 4 TEAEs reported.

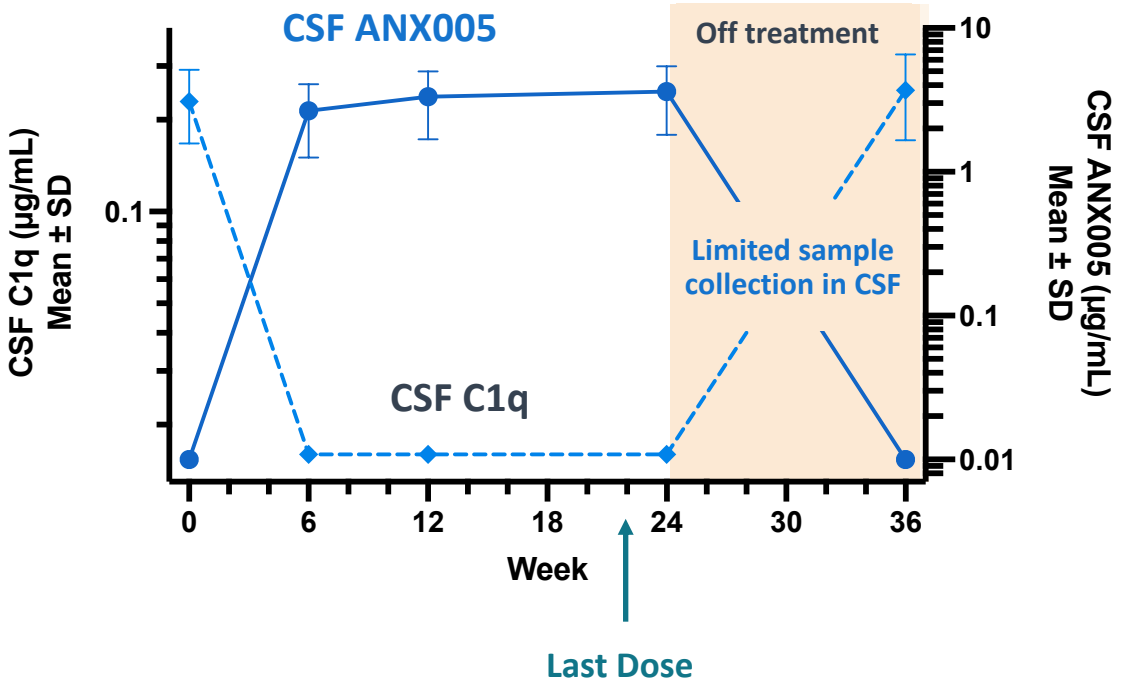
ANX005 Demonstrated Rapid & Sustained Target Engagement in Blood and CSF

Drug Present 4-10 weeks Post Last Dose in Serum

Full Target Engagement in Serum (n=23)



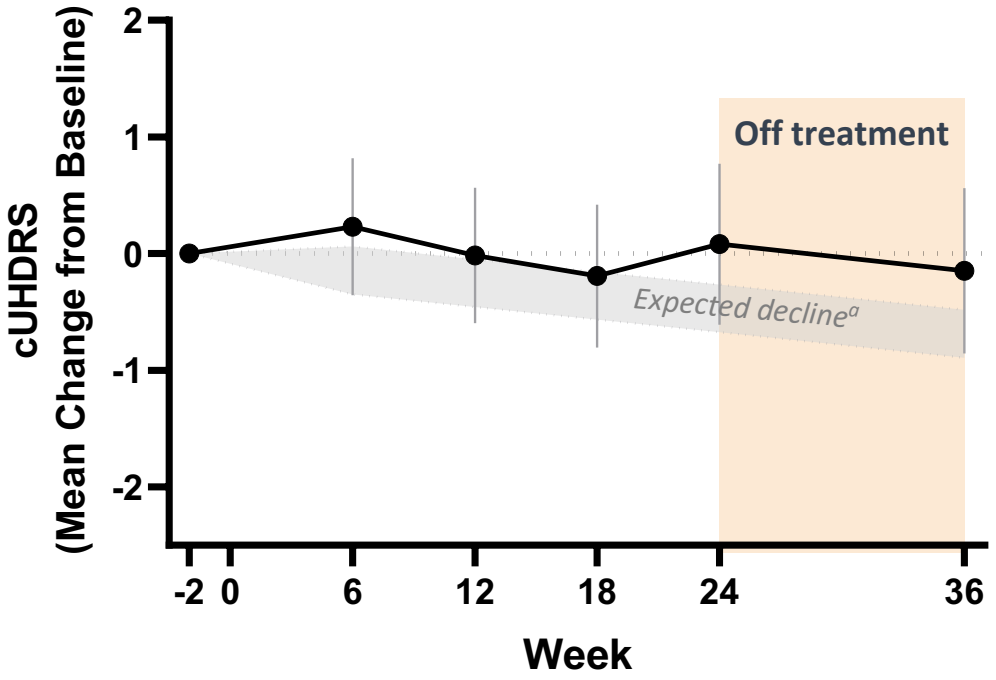
Full Target Engagement in CSF (n=23)



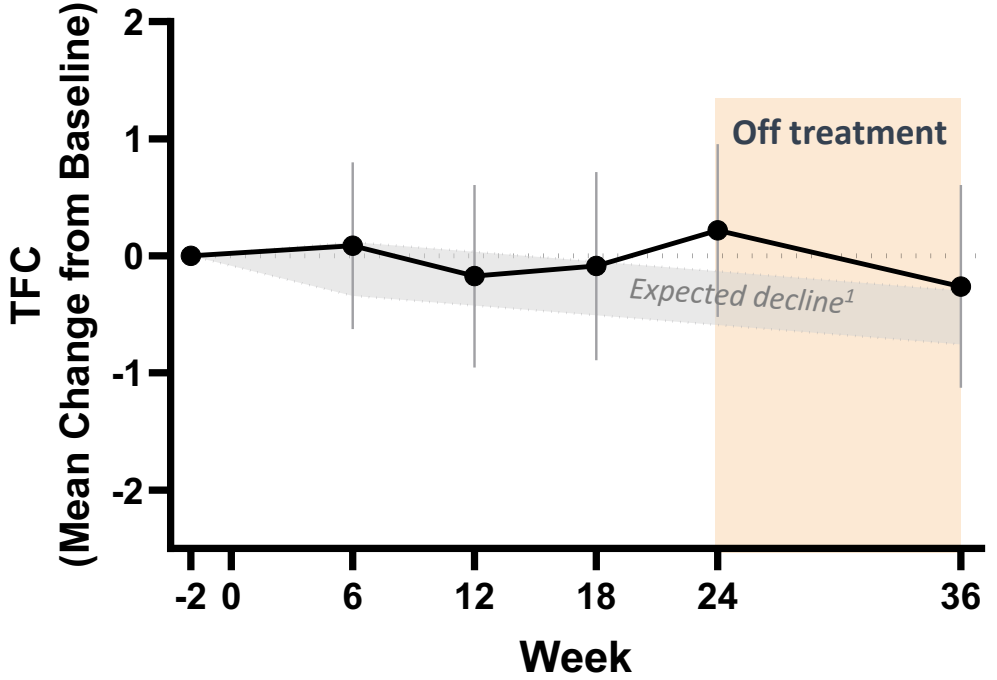
Drug levels in CSF were consistent with expectations, being ~0.2% of serum drug levels

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)

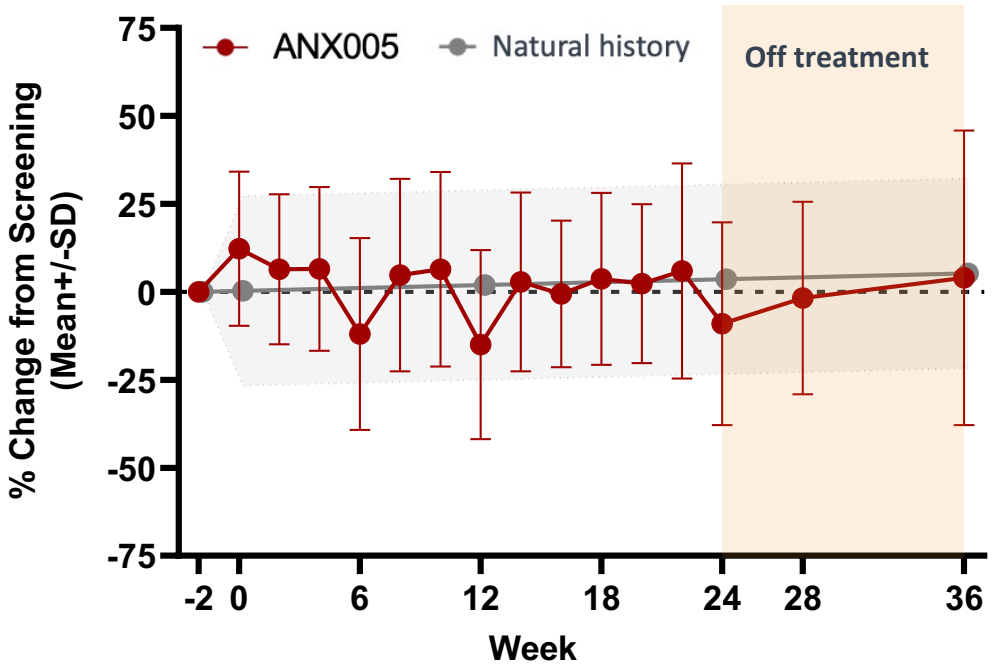


MMRM; LS means +/- 95% CI

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

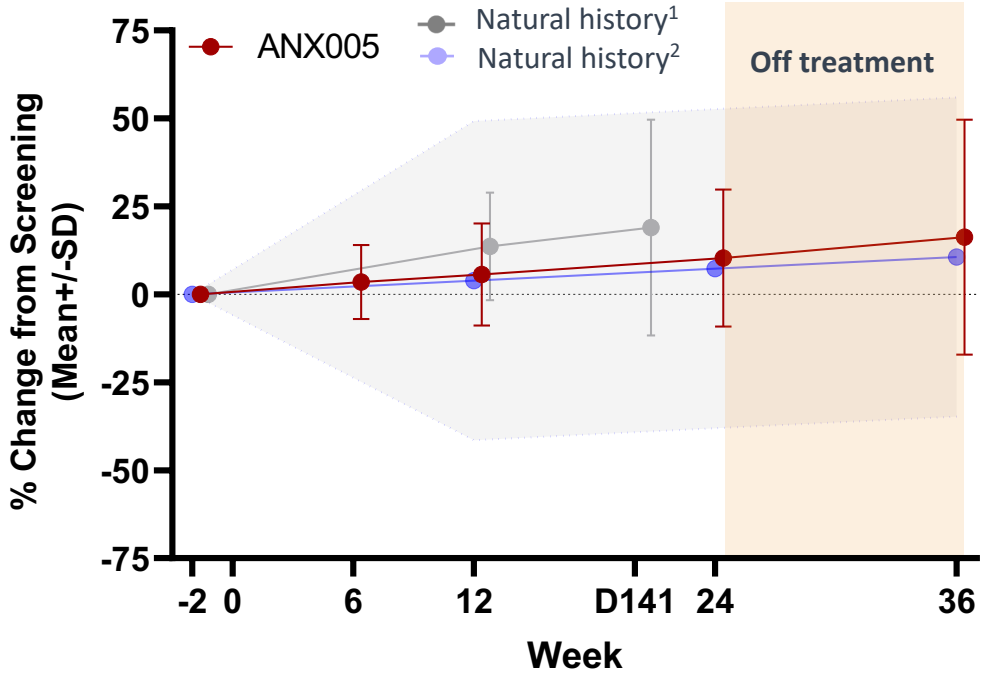
NfL Changes Stable and Consistent with Natural History Through On- and Off-Treatment Periods (9 months)

Plasma NfL (n=23)



[1]Interpolated data for manifest cohort, Rodrigues et al., Sci Transl Med. 2020;12(574).

CSF NfL (n=23)

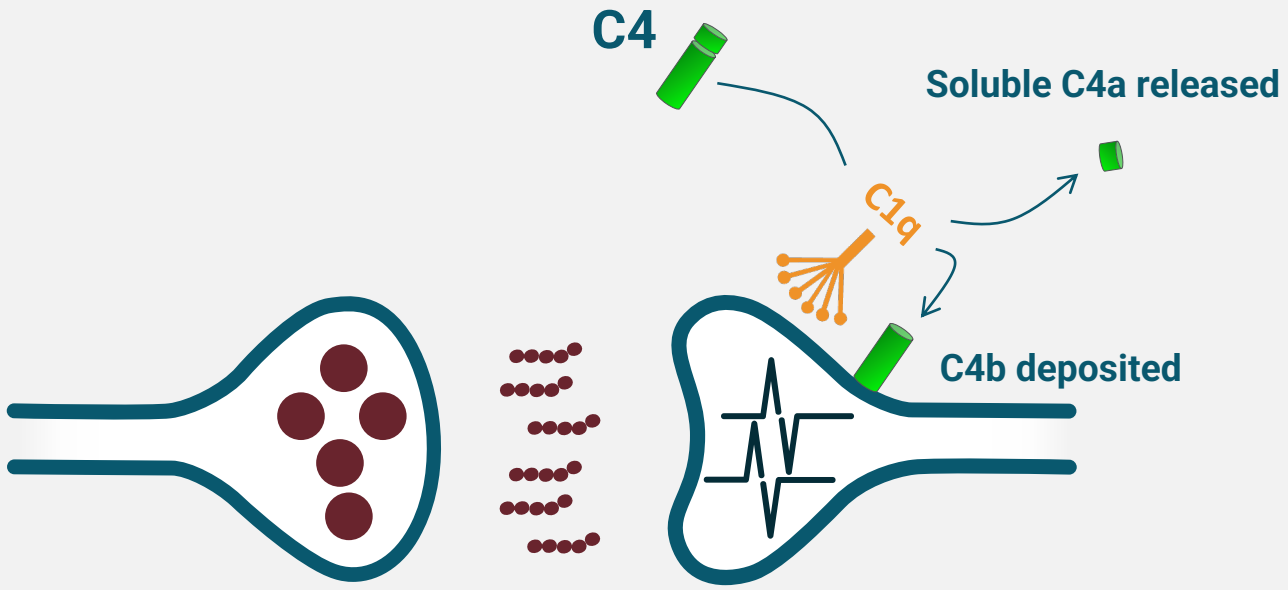


[1]Tabrizi, NEJM 2019, 38:2307
[2]Interpolated from Rodrigues et al., Sci Transl Med. 2020;12(574).

CSF C4a/C4 ratio: A Sensitive Measure of Ongoing Complement Activation that Corrects for Genetic Variation Between Patients

First complement precision medicine approach in Huntington's disease

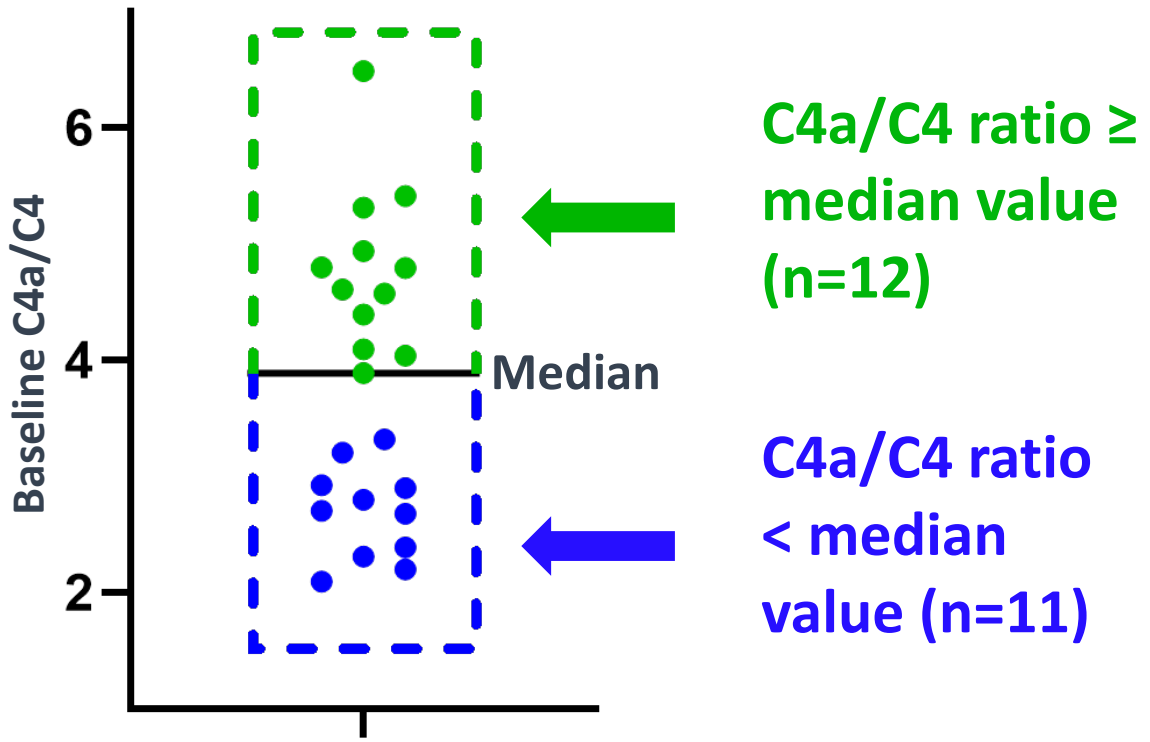
1. C1q binds to synapses, and C4 is the first complement component targeted by the activated C1 complex.
2. C4 is broken down (decreases), and C4a is released (increases)
3. CSF C4a has been shown to be elevated and increases with HD progression[a]
4. Measurement of C4 and its activation product C4a as a ratio in CSF might be helpful in identifying populations most likely to respond to anti-C1q therapy



[a]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.

Median Baseline C4a/C4 Levels in CSF Used to Define Patients with High vs Low Complement Activity in HD Study

C4a/C4 ratios for the total study population

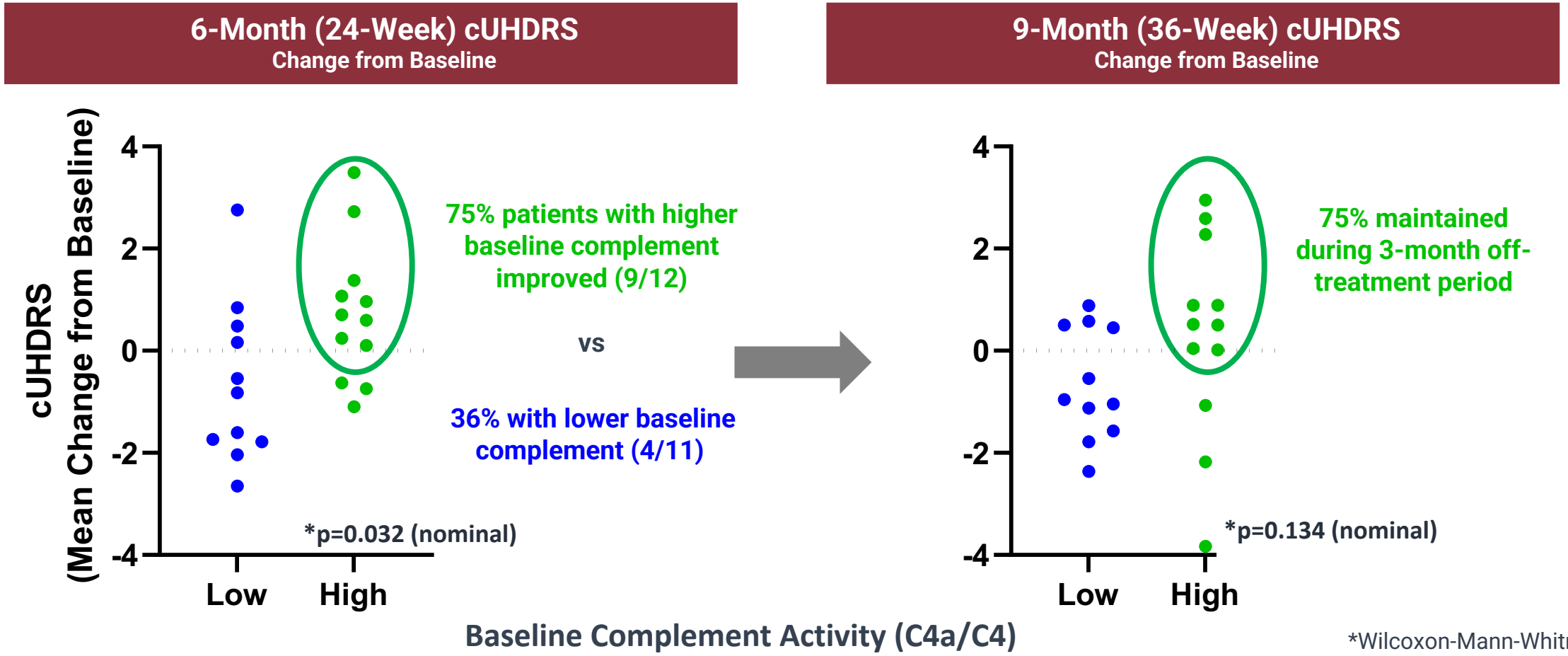


- Objective assessment of outcomes grouped by baseline complement levels
- Patients, investigators & sponsor blinded to C4a/C4 levels
- Baseline demographics evenly matched between patients with higher and lower CSF complement activation

*C4a levels divided by levels of C4 (C4a/C4 ratio) to normalize genetic variability in C4 gene copy number
*Post hoc analysis, p-values nominal for high/low comparisons

75% of Patients with Elevated Baseline Complement Levels Improved at Week 24 and Maintained Through Follow-Up Period

Twice as many patients with elevated complement improved compared to subjects with lower activity

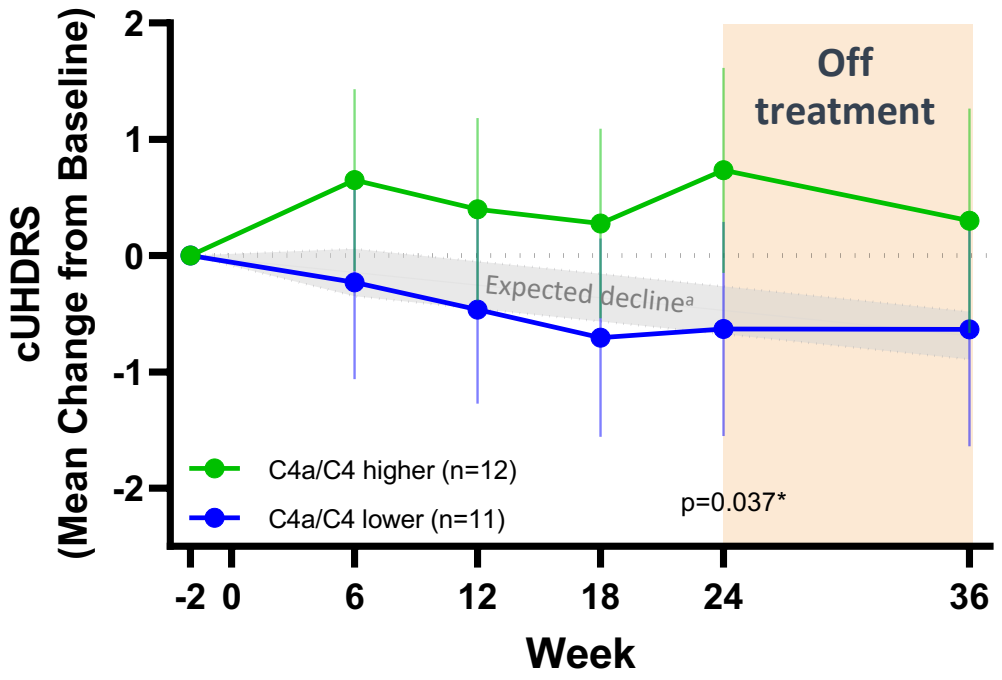


*Wilcoxon-Mann-Whitney Test

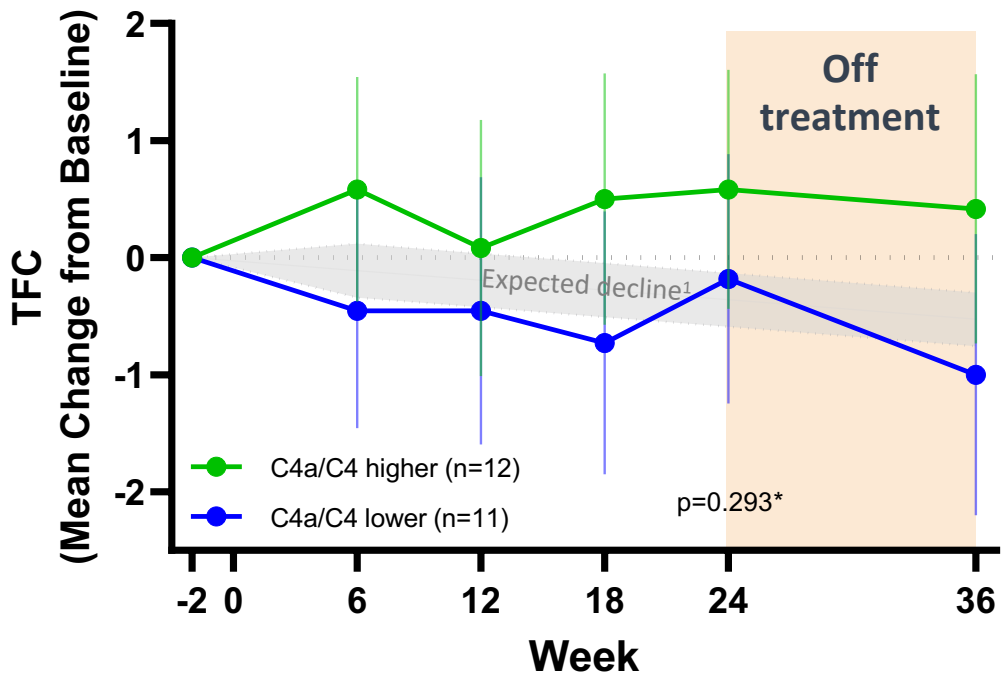
Baseline demographics evenly matched between patients with higher and lower CSF complement activation

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)

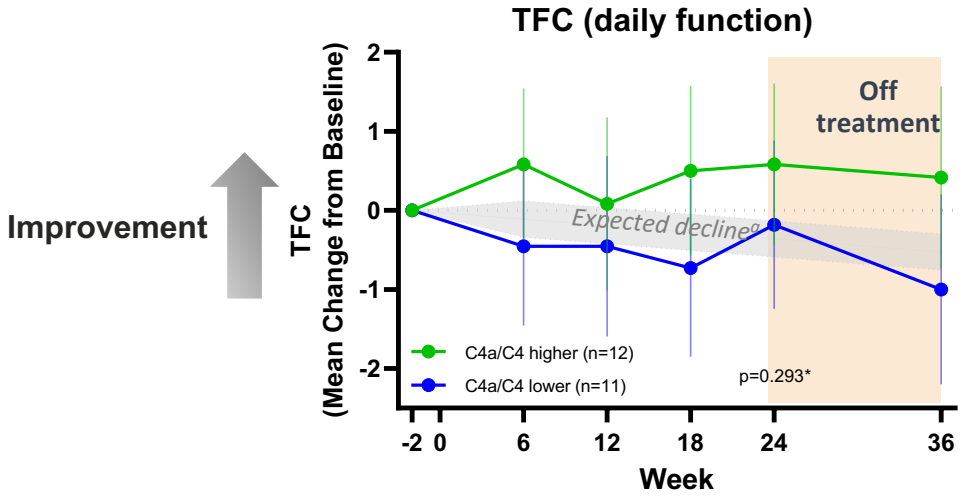


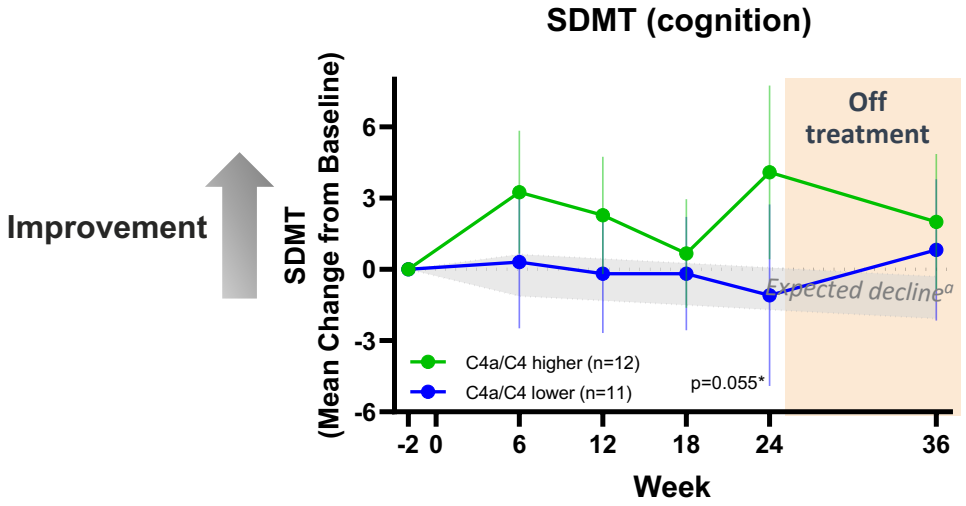
Benefit at All Time Points in High Complement Group (TFC)

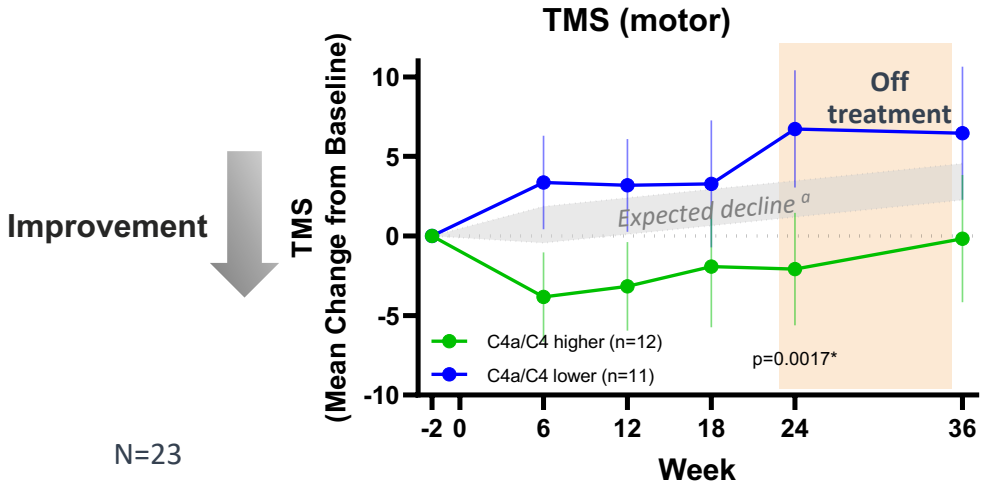


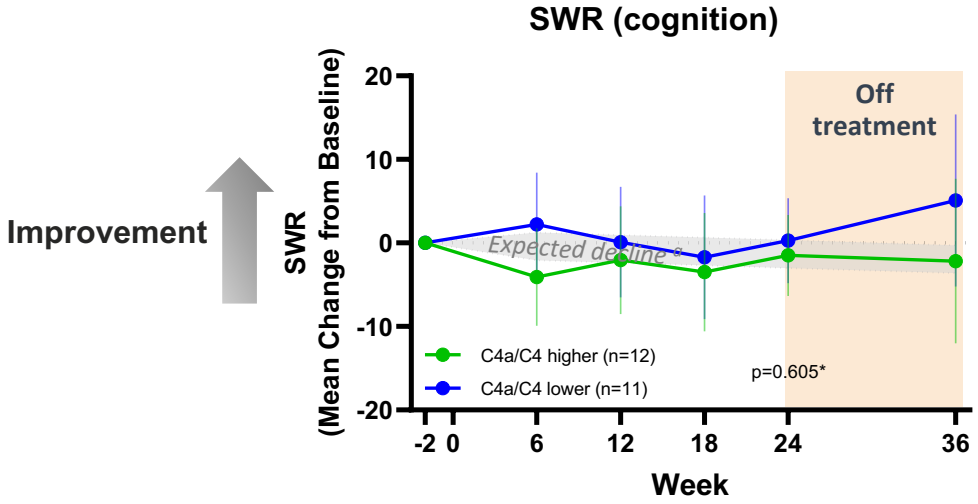
*Comparing higher vs lower C4a/C4 groups at week 2; MMRM; LS means +/- 95% CI; N=23.
[a]Expected decline = interpolated natural history from Schobel 2017 (TRACK-HD).

Rapid and Sustained Separation Generally Shown in Patients with Higher Baseline Complement Activity Across Most cUHDRS Domains









N=23

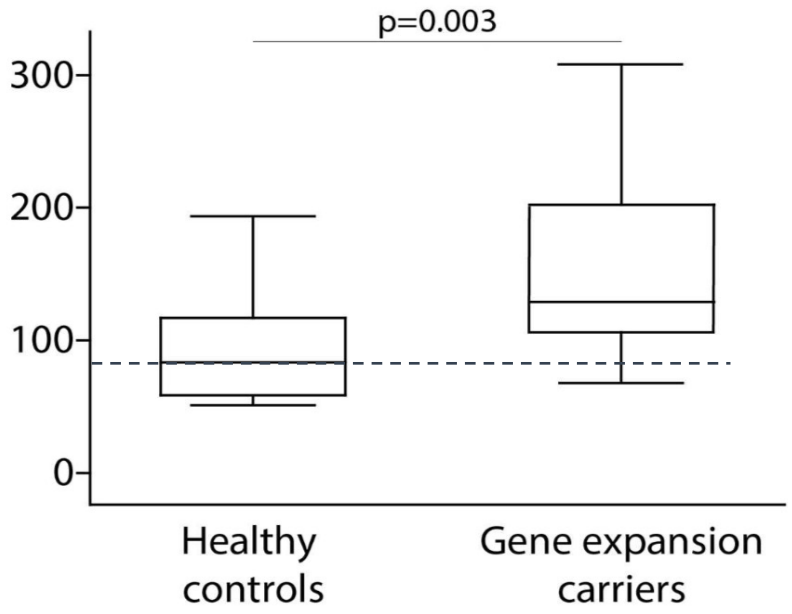
All 4 domains of cUHDRS

- Most showed rapid improvement and sustained effect
- Early separation sustained both on and off-treatment

*MMRM; LS means +/- 95% CI; Comparing higher vs. lower groups at week 24.
[a]Interpolated natural history from Schobel 2017 (TRACK-HD).

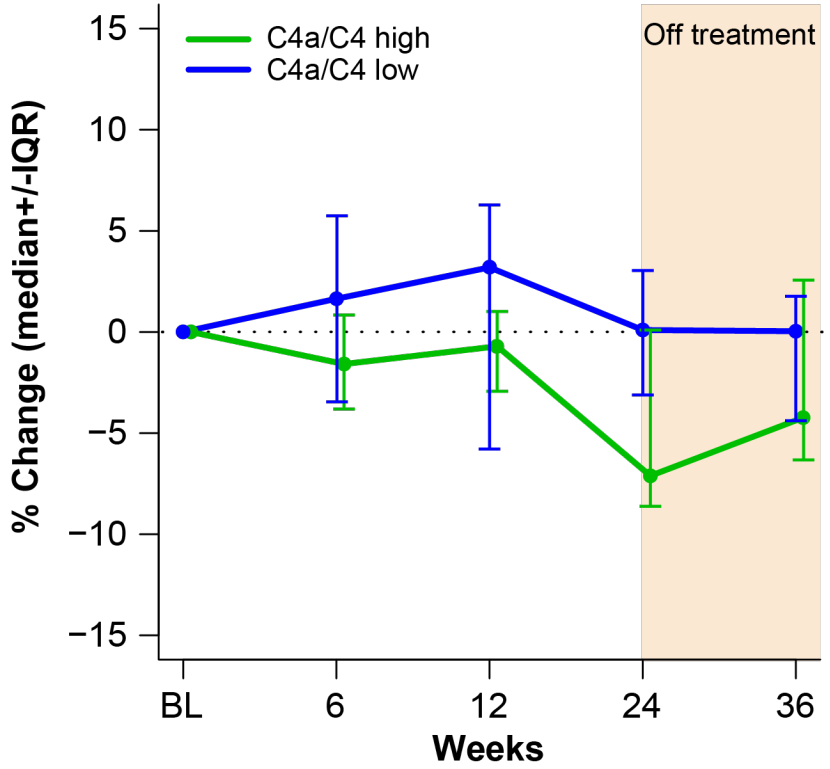
Independent Marker of Inflammation in HD (YKL-40[a]) Decreased in ANX005-treated Patients Exhibiting Clinical Improvement

YKL-40 Increased in CSF of HD Patients



Rodrigues *PLoS One*. 2016;11:e0163479

YKL-40 Reduced in Patients with High Baseline Complement Activity (C4a/C4)



Annexon data on file

[a]Produced by activated glia - Elevated in HD and other neurological diseases

Positive ANX005 HD Phase 2 Results Support Continued Advancement

Phase 2 HD Trial Findings

- ✓ Full C1q target engagement in blood and CSF into follow-up period
- ✓ Stabilized disease progression in full cohort over 9-month study
- ✓ Rapid, sustained clinical improvement in patients with higher baseline complement activity over 9-month study
- ✓ Generally well-tolerated with favorable benefit-risk profile; enhanced safety management approach
- ✓ Widely-studied MOA; first clinical application demonstrating that blocking aberrant complement activity at its source may protect synapses in patients with HD
- ✓ NfL changes stable and consistent with natural history through on- and off-treatment periods (9 months)

Next Phase 2/3 Study in Early Manifest HD Expected to Initiate in 2023