

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

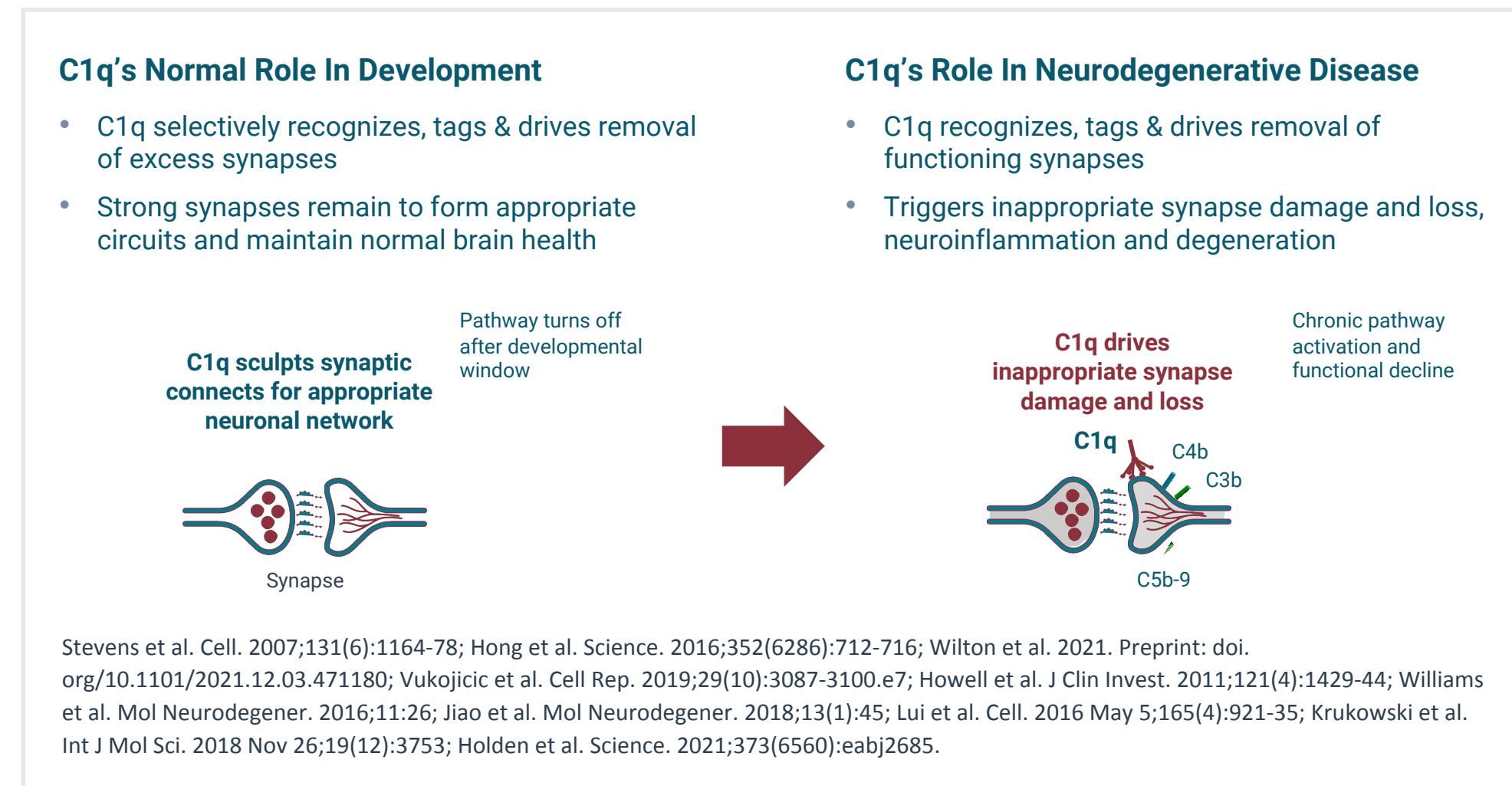
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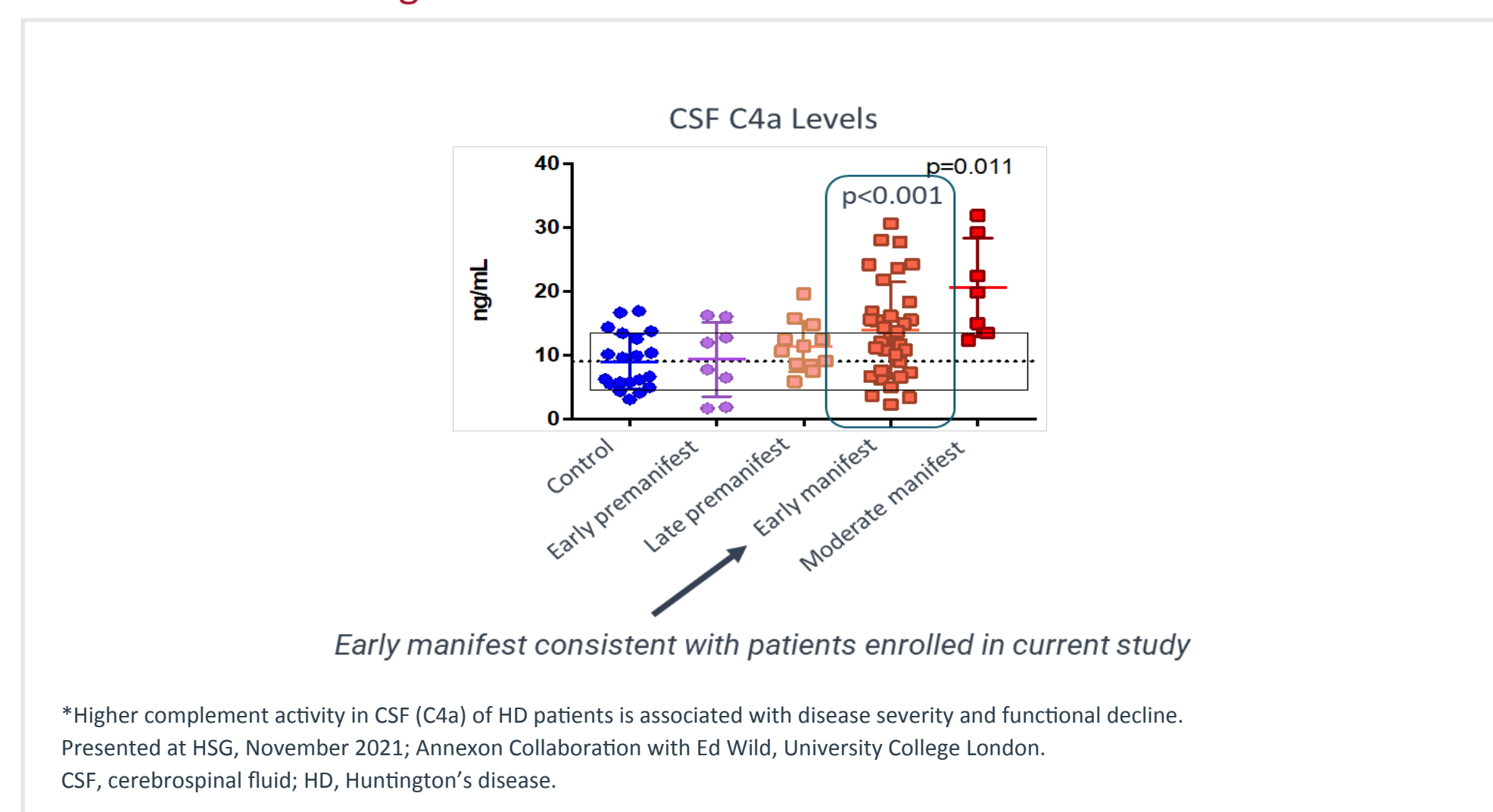
## Background

- Increased complement activation has been implicated in synapse elimination, neuroinflammation, and neurodegeneration in disorders such as Huntington's disease (HD) (Figures 1-2)

**Figure 1. C1q / Classical Complement Play A Normal Role in Development that is Reactivated in Neurodegenerative Disease**



**Figure 2. C4a Levels in Cerebrospinal Fluid Are Elevated in HD Patients and Increase With HD Progression\***

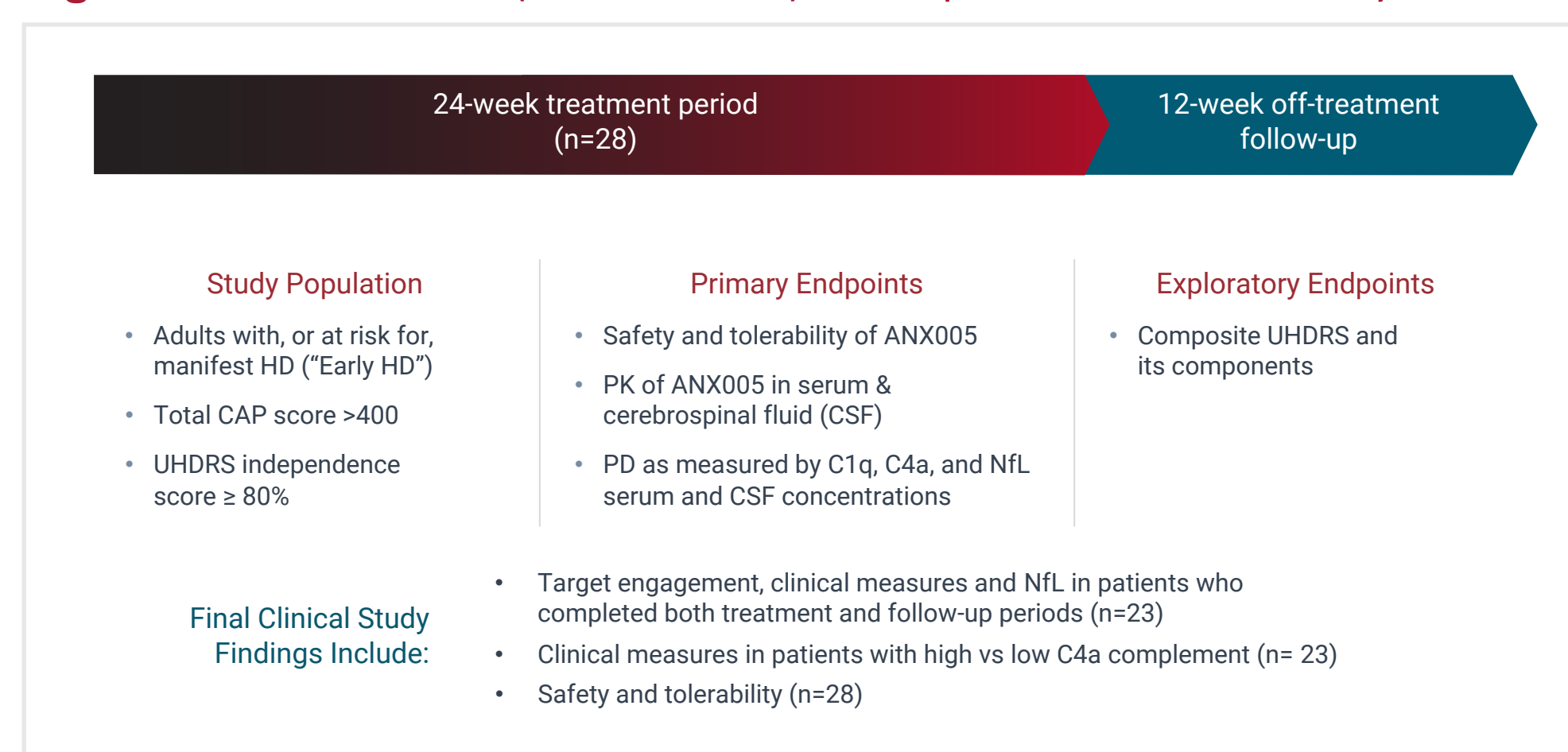


- ANX005, a humanized monoclonal antibody targeting C1q, was designed to inhibit the classical complement pathway, potentially preserving synapses to improve neuronal function and prevent subsequent neurodegeneration
- Systemic administration of an antibody against C1q reduced complement deposition at the level of the synapse and prevented synapse loss in mice expressing mutant huntingtin (Wilton et al. 2021. Preprint. doi.org/10.1101/2021.12.03.471180)
- Here, we report final results from ANX005-HD-01, a phase 2 study of patients with or at risk for manifest HD

## Methods/Techniques

- ANX005-HD-01 (NCT04514367) was a multicenter, open-label, phase 2 study evaluating ANX005 in patients who had, or were at risk for, manifest HD
- In ANX005-HD-01, eligible patients (CAP >400, Independence ≥80%) received 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, with follow-up visits on Weeks 24, 28, and 36 (Figure 3)

**Figure 3. ANX005-HD-01 (NCT04514367) Is An Open-Label Phase 2 Study**



- Endpoints were assessed in the on-treatment period through Week 24 and in the off-treatment follow-up period through Week 36
- Primary objectives included safety/tolerability, pharmacokinetics (PK) in cerebrospinal fluid (CSF) and serum, and pharmacodynamics as measured by C1q, C4a, and neurofilament light chain (NFL) levels (CSF and plasma)
- Exploratory objectives of clinical efficacy included composite Unified Huntington's Disease Rating Scale (cUHDRS) and its components
  - The cUHDRS combines four domains: Total Functional Capacity (TFC), Total Motor Score (TMS), Symbol Digit Modalities Test (SDMT) and Stroop Word Reading (SWR)

## Results/Outcome

- In total, 28 patients received at least one dose of ANX005 and were evaluable for safety and tolerability; 23 patients completed both the treatment and follow-up periods (Table 1)
- In the safety population, the mean age was 49.7 years, and the mean CAP score was 505.7
- Approximately 90% of patients had early manifest HD; the remaining patients were pre-manifest

**Table 1. Baseline Demographic Characteristics Were Consistent With Prior HD Natural History Study Cohorts**

Study participant characteristics	All patients (N=28)	Treatment completers (N=23)	TRACK-HD <sup>a</sup> (N=123)
Age, years, mean (SD)	49.7 (12.5)	48.5 (13.3)	48.8 (9.8)
Female, %	43	35	45
CAG repeat length, mean (SD)	44.6 (3.5)	45.1 (3.7)	43.7 (3.0)
CAP score, mean (SD)	505.7 (57.9)	512.2 (60.4)	NR
Manifest HD, n (%)	25 (89)	21 (91)	123 (100)
CSF C4a, ng/mL, mean (SD)	13.9 (8.2)	15.0 (7.0)	NR
Baseline plasma NFL, pg/mL, mean (SD)	40.1 (13.7)	41.3 (13.3)	NR
Baseline CSF NFL, pg/mL, mean (SD)	3104.1 (810.8)	3236.0 (816.8)	NR
cUHDRS, mean (SD)	10.4 (3.2)	10.1 (2.9)	11.7 (2.9)
TFC, mean (SD)	10.6 (2.2)	10.4 (2.3)	10.9 (2.0)
Total Motor Score, mean (SD)	21.6 (12.6)	22.3 (11.4)	23.7 (10.8)
Symbol Digit Modalities Test, mean (SD)	29.7 (11.3)	28.8 (11.0)	33.6 (10.2)
Stroop Word Reading Test, mean (SD)	59.0 (18.7)	56.7 (16.7)	78.3 (19.5)

<sup>a</sup>Based on the TRACK-HD natural history study (Schobel et al. Neurology. 2017;89(24):2495-2502). For illustrative purposes only—differences in patient demographics, study designs, and other factors exist, and caution should be exercised when comparing data across studies.

CAG, cytosine-adenine-guanine; CAP, CAG age product; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's disease; NFL, neurofilament light chain; NR, not reported; SD, standard deviation; TFC, Total Functional Capacity.

## Treatment-Emergent Adverse Events

- All safety population patients experienced transient infusion-related reactions during the first dose, mainly transient maculopapular rash (Table 2)
- Five treatment discontinuations occurred
  - Two treatment discontinuations were deemed unrelated to drug (COVID-19, consent withdrawn)
  - Three treatment discontinuations were deemed potentially related to drug; all reversed or improved upon treatment discontinuation (two serious adverse events of lupus-like presentation and idiopathic pneumonitis, and one adverse event of asymptomatic hemolytic anemia)

**Table 2. ANX005 Was Generally Well-Tolerated**

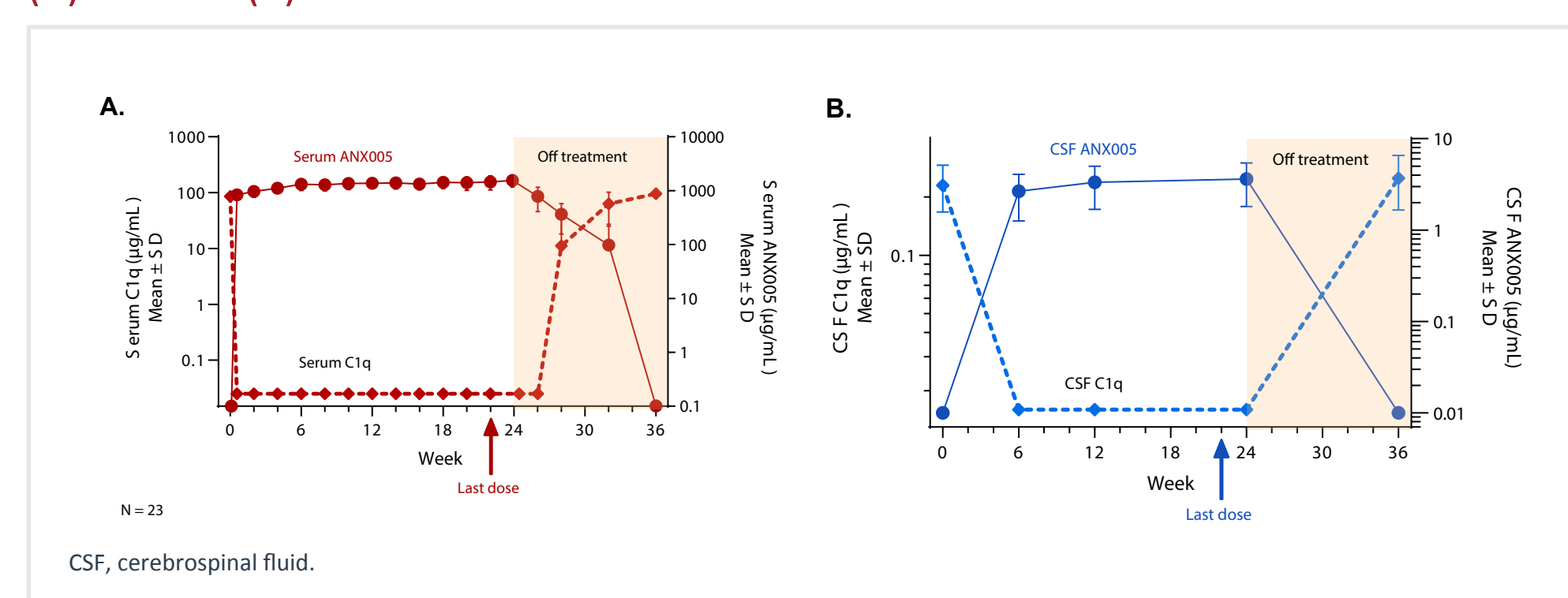
n (%)	Safety population (N=28)	
	All grades	Grade 3
Any reported TEAE	28 (100)	12 (43)
Most common TEAE		
Infusion-related reaction (IRR)	28 (100)	8 (29)
Most common TEAEs (non-IRR)	25 (89)	6 (21)
Dizziness	5 (18)	0 (0)
Nausea	5 (18)	0 (0)
Headache	4 (14)	0 (0)
Vomiting	4 (14)	0 (0)
COVID-19	4 (14)	0 (0)
Rash	4 (14)	1 (4)
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)

No grade 4 TEAEs reported. Treatment-emergent adverse events were considered common if they occurred in at least 4 subjects.

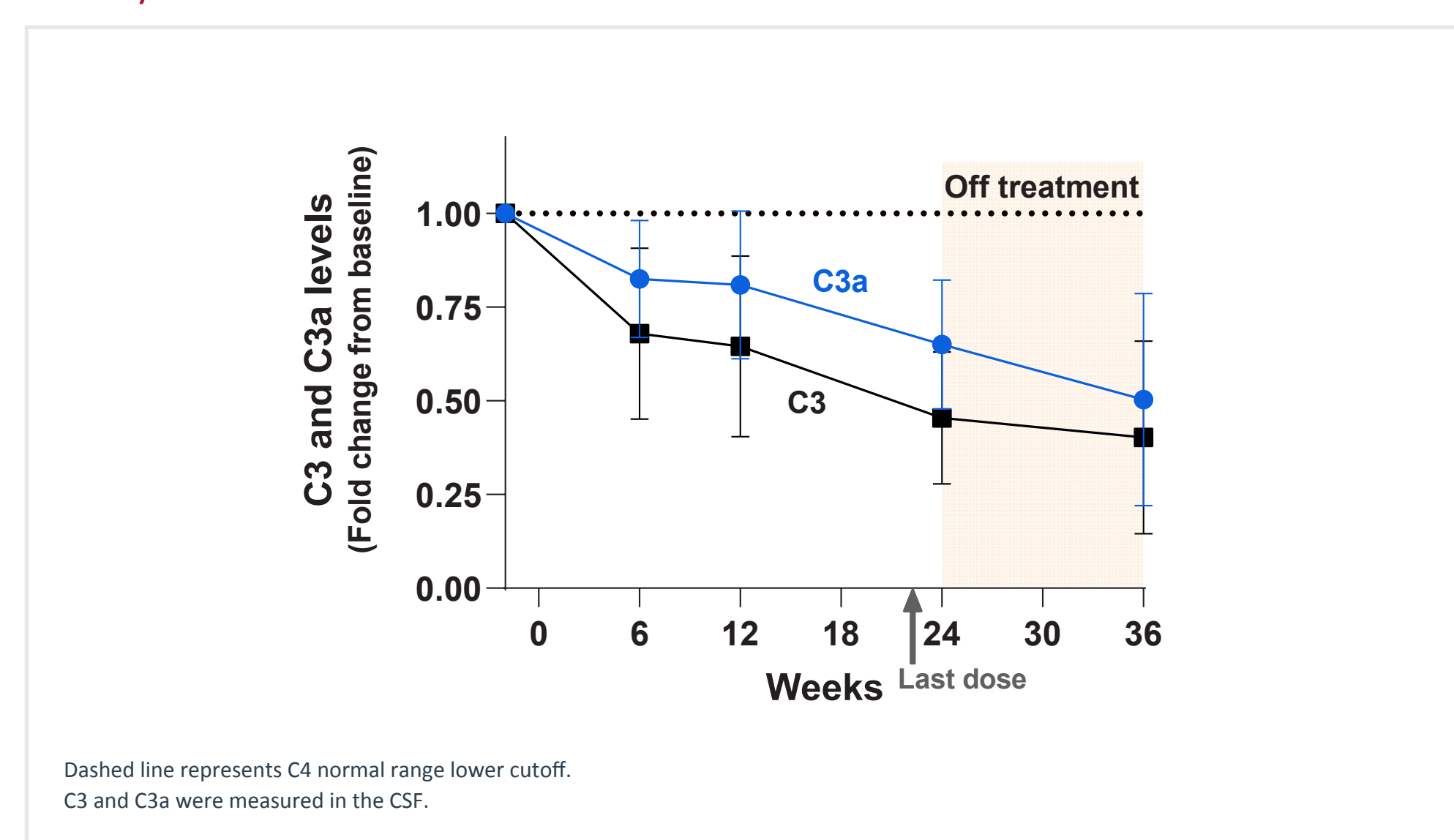
TEAE, treatment emergent adverse event.

- Steady-state PK were achieved in the serum and CSF by Week 6 (Figure 4)

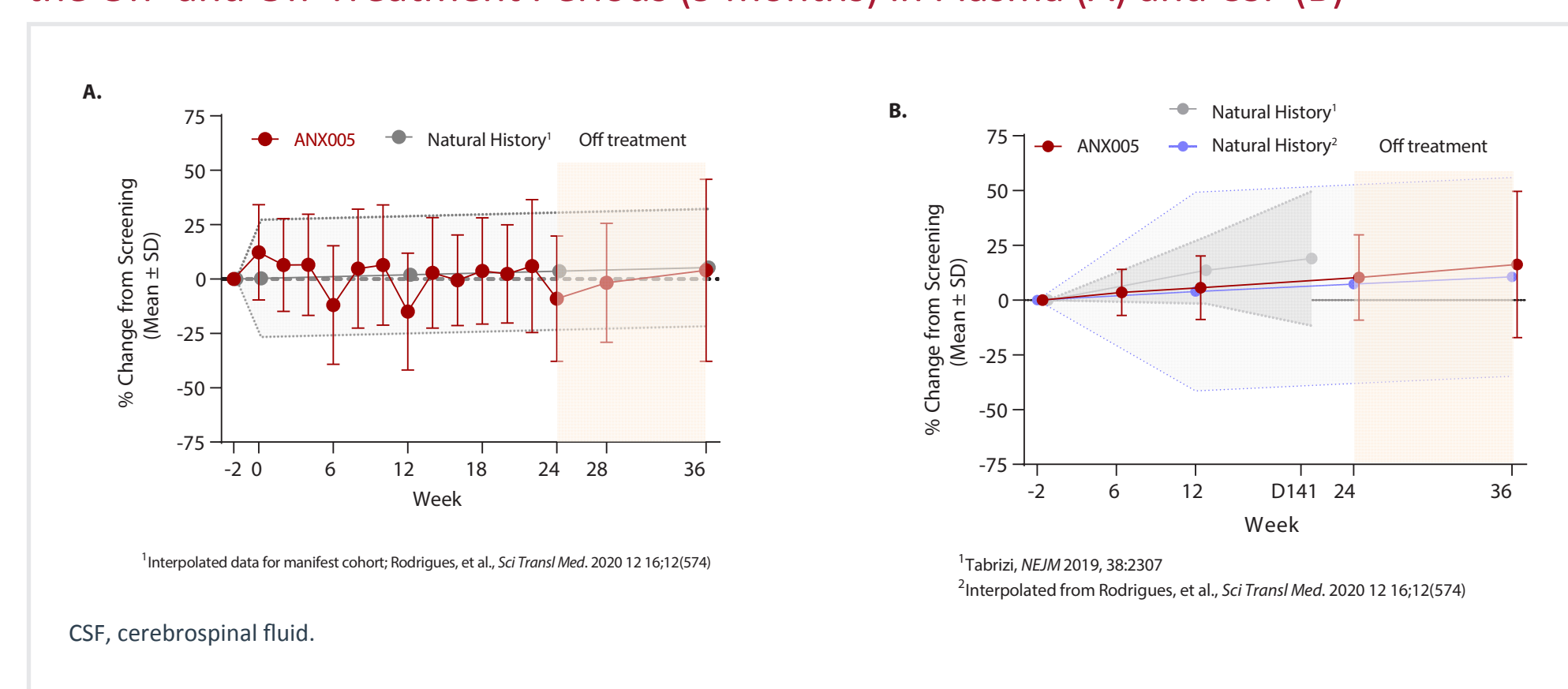
**Figure 4. ANX005 Demonstrated Rapid & Sustained Target Engagement in Serum (A) and CSF (B)**



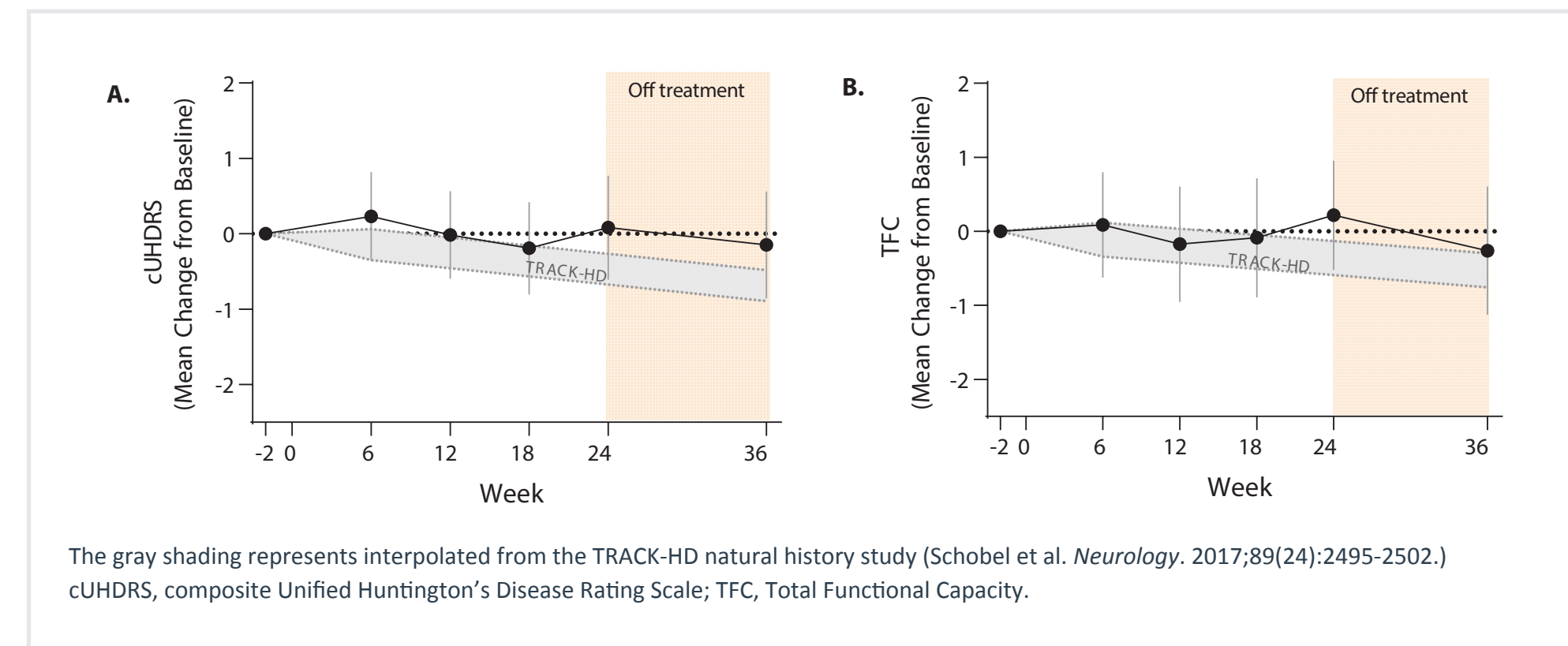
**Figure 5. ANX005 Had A Prolonged Drug Effect on the Complement System in the Brain; Reductions in C3a and C3 Are Suggestive of ANX005's Inhibitory Effects on Astrocytes and Reduced Neuroinflammation**



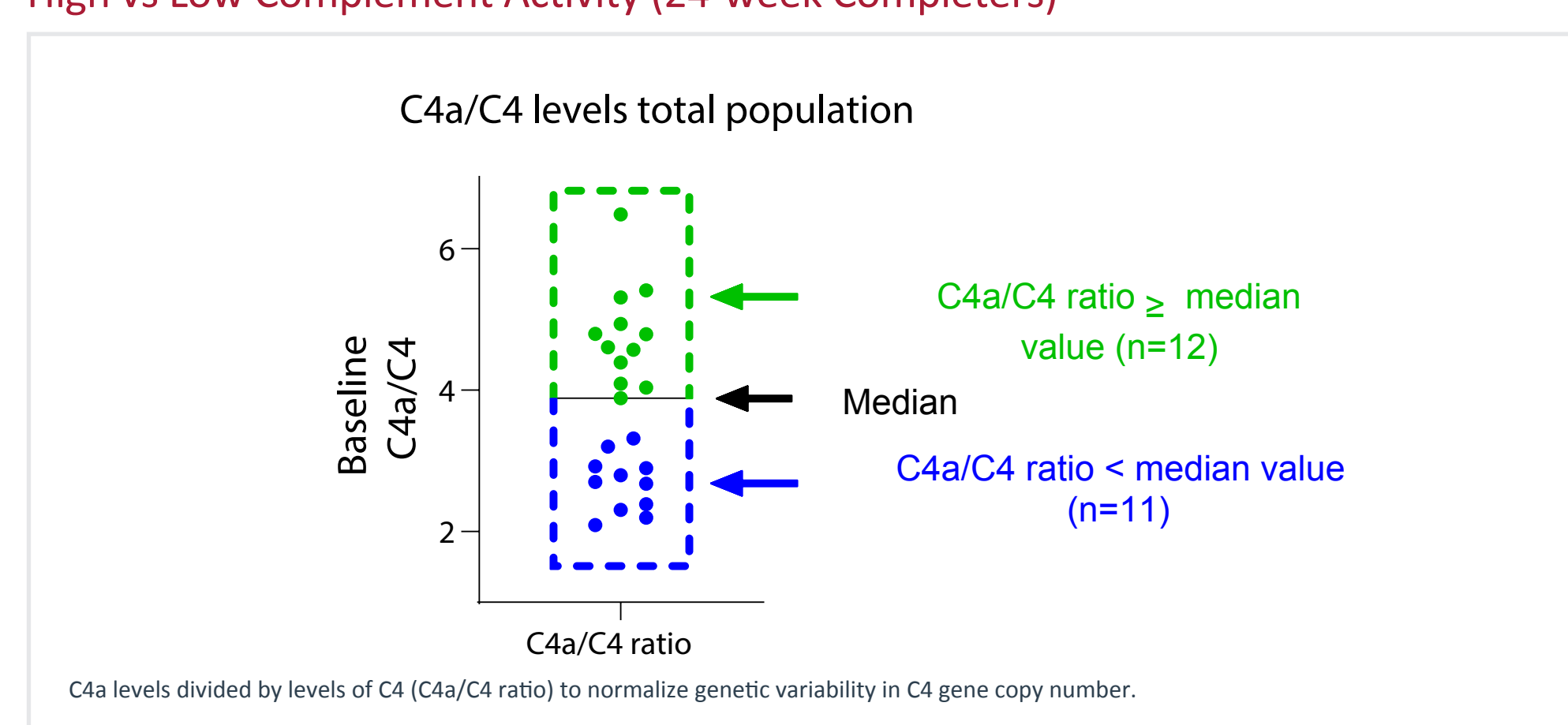
**Figure 6. NFL Changes Were Stable and Consistent With Natural History Through the On- and Off-Treatment Periods (9 months) in Plasma (A) and CSF (B)**



**Figure 7. Clinical Disease Progression Was Stable in Overall Patient Population Through Entire 9-month Study as Measured by Mean Change in cUHDRS (A) and TFC (B)**



**Figure 8. Median Baseline C4a/C4 Ratios in CSF Were Used to Define Patients With High vs Low Complement Activity (24-week Completers)**

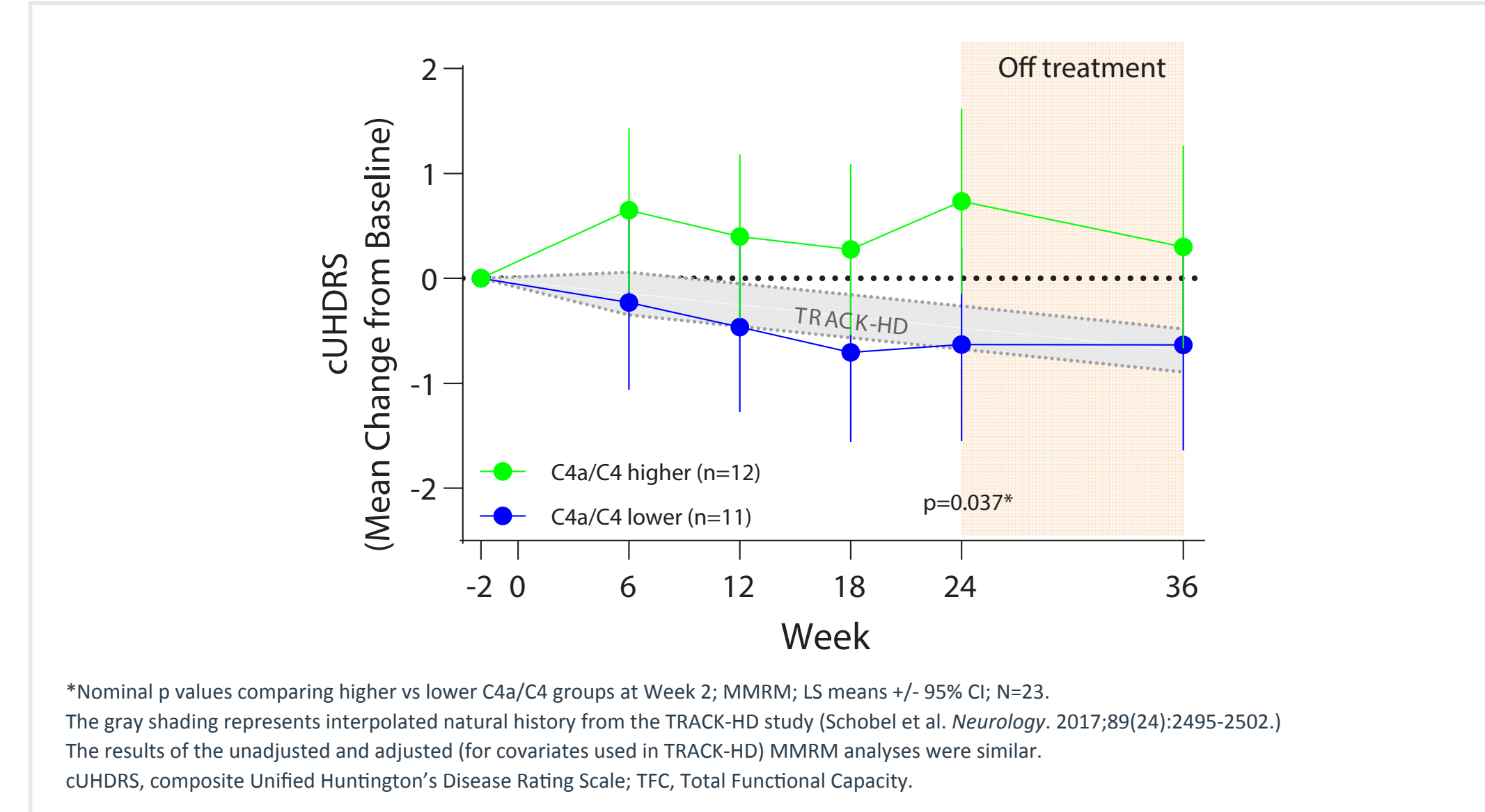


**Table 3. Baseline Demographics Were Well Balanced Between Patients with Higher and Lower C4a/C4 CSF Complement Activation**

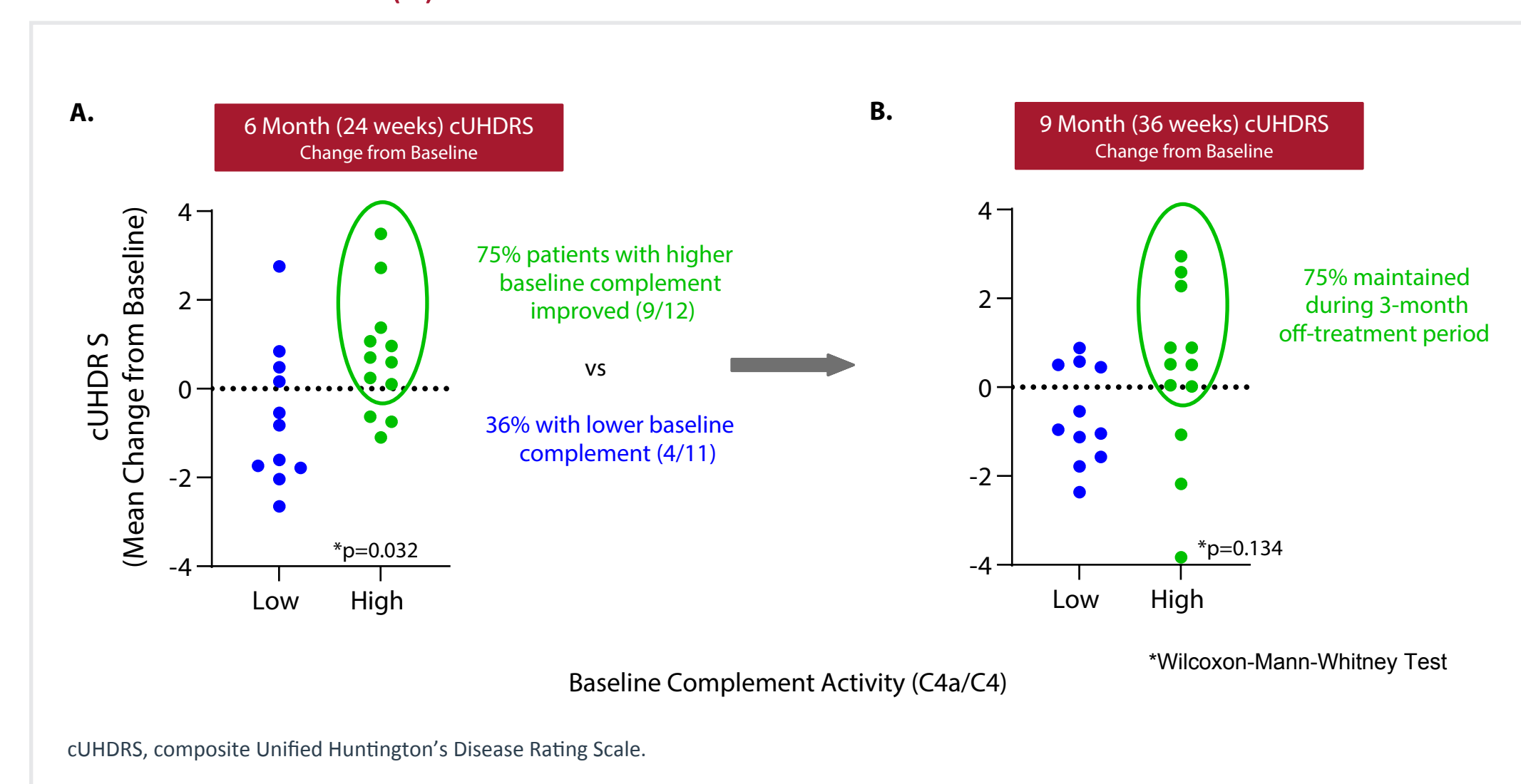
HD-01 characteristics, mean (SD)	C4a/C4 low (n=11)	C4a/C4 high (n=12)
cUHDRS	10.3 (3.0)	9.8 (2.9)
TFC	10.5 (2.3)	10.3 (2.4)
TMS	19.7 (10.9)	24.7 (11.8)
SDMT	30.2 (11.9)	27.5 (10.5)
SWR	54.7 (14.5)	58.6 (19)
CAG repeats	45.7 (4.2)	44.5 (3.1)
Age, years	46.6 (15.5)	50.2 (11.2)
CSF NFL, ng/mL	3334 (861)	3146 (801)

CAG, cytosine-adenine-guanine; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; SWR, Stroop Word Reading; SDMT, Symbol Digit Modalities Test; TFC, Total Functional Capacity; TMS, Total Motor Score.

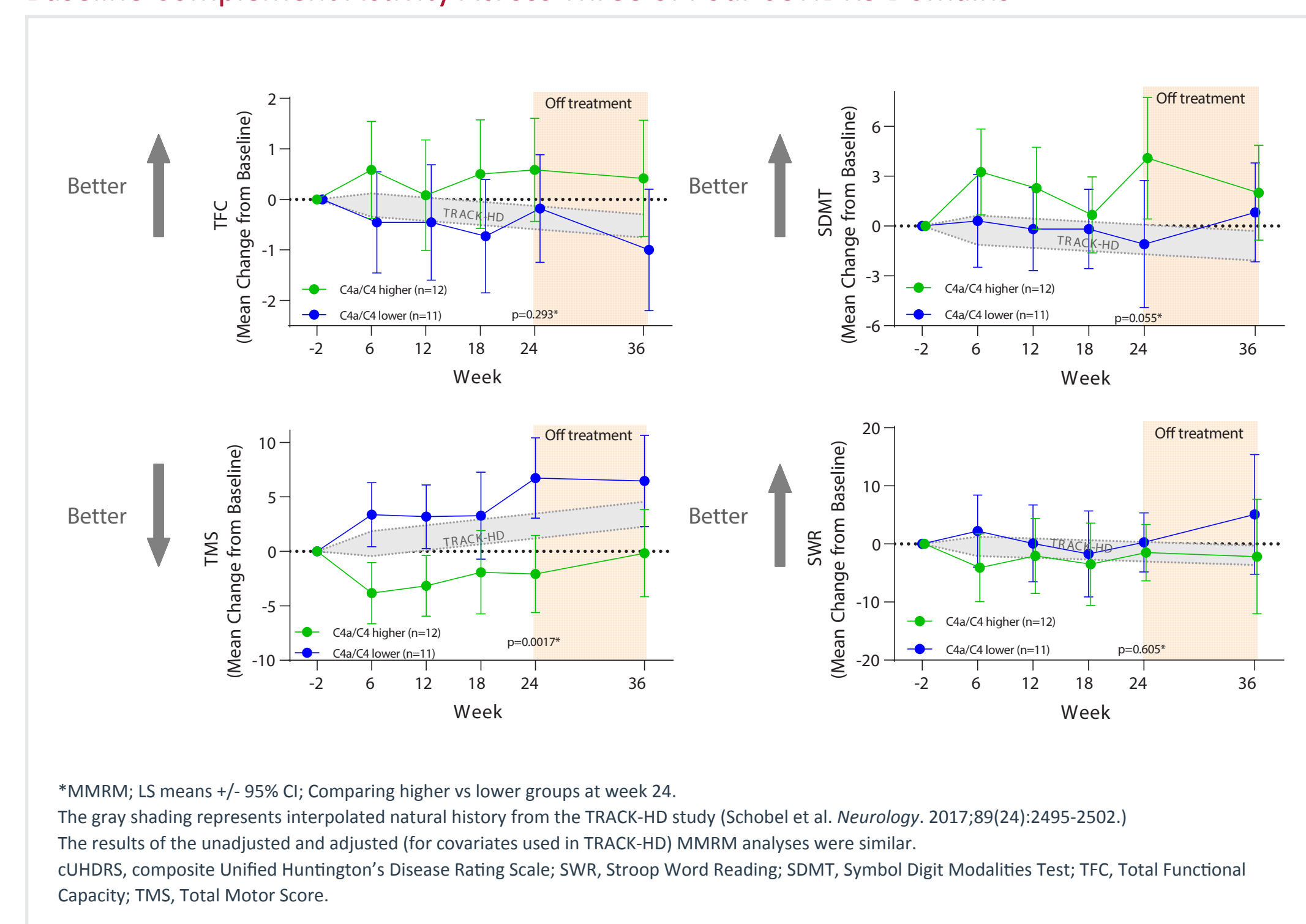
**Figure 9. Patients With High Baseline C4a/C4 Exhibited Clinical Improvement Over Baseline Throughout the Study, With A Significant Difference From Patients With Low Baseline C4a/C4 at Week 24; Patients With Low Baseline C4a/C4 Showed A Clinical Decline Similar to Natural History**



**Figure 10. 75% of Patients Exhibiting High Baseline Complement Activity (C4a/C4) Showed Improvement in cUHDRS at Week 24 (A), Which Was Maintained Through the Off-treatment Period (B)**



**Figure 11. Rapid and Sustained Separation Was Generally Shown in Patients With Higher Baseline Complement Activity Across Three of Four cUHDRS Domains**



## CONCLUSIONS

- ANX005 was generally well-tolerated, with a favorable benefit-to-risk profile in HD
- Full C1q inhibition was maintained in the body & CNS through the on-treatment and off-treatment periods
- Clinical improvements persisted in patients with higher baseline complement through the on-treatment and into the off-treatment periods (9 months)

## Disclosures:

RK: employment with Research Catalyst, LLC; consultancy/advisory role with US WorldMeds, paid to institution; research funding from US WorldMeds, paid to institution; speakers bureau with Supernus; Scientific Advisory or Data Safety Monitoring board for Impel Pharma.

DC: consultancy/advisory role with HD Insights, Lundbeck, Spark, and Teva Neuroscience; research funding from AbbVie, CHDI, Department of Defense, Genentech/Roche, Griffin Family Foundation, HDUSA, Neurocrine, NIH, and Vaccinex, paid to institution; Scientific Advisory or Data Safety Monitoring board for Teva Neuroscience and Wave Life Sciences.

AM, BDH, PL, LT, PC, TY & HK: employment with and equity ownership in Annexon Biosciences, Inc.

EC-M: employment with Annexon Biosciences and Biogen, Inc.; equity ownership in Annexon Biosciences, Inc.

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