Phase 2 study evaluating safety, pharmacokinetics/pharmacodynamics, biomarkers, and efficacy of ANX005 in patients with Huntington's disease

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Abstract

Objective: To assess the safety, PK/PD, exploratory biomarkers, and efficacy of ANX005 in patients with, or at risk for, manifest HD.

Background: Increased complement activation has been implicated in synapse elimination, neuroinflammation, and neurodegeneration in disorders such as HD. 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.

Methods: Eligible patients (CAP score >400) enrolled in this multicenter, open-label, phase 2 study (NCT04514367) received intravenous dosing of ANX005 every 2 weeks through Week 22. Patients who received ≥1 dose were included in the safety analysis (n=28). Primary objectives included safety, tolerability, and drug, C1q, and neurofilament light chain (NfL) levels in blood and cerebrospinal fluid (CSF). Exploratory objectives included complement activity and change in composite Unified Huntington's Disease Rating Scale (cUHDRS) as a measure of clinical efficacy.

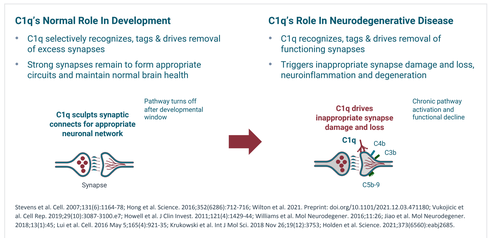
Results: Interim results from this ongoing phase 2 trial show that ANX005 was generally well tolerated, with full target engagement of C1q in serum and CSF. All patients experienced an infusion related reaction, 93% occurred on day 1 and 96% were primarily rashes (27/28). There were 2 serious AEs (systemic lupus erythematosus and idiopathic pneumonitis), which resolved or stabilized upon drug discontinuation. In total, 56% (13/23) of patients who completed 24 weeks of treatment demonstrated improved clinical function as measured by change in cUHDRS from baseline. 75% of patients (9/12) exhibiting high baseline complement activity (C4a/C4) improved in cUHDRS, compared with 36% of patients (4/11) with low baseline complement activity. Changes in mean plasma and CSF NfL levels appeared consistent with disease natural history.

Conclusions: These results support a novel role for complement activation in HD and indicate the potential for disease modification with continued development of ANX005. Off-drug observation from Week 24 to 36 is ongoing.

Background

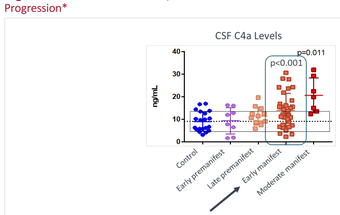
- Increased complement activation has been implicated in synapse elimination, neuroinflammation, and neurodegeneration in disorders such as Huntington's disease (HD) (**Figures 1-2**)

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



Stevens et al. Cell. 2007;131(6):1164-78; Hong et al. Science. 2016;352(6286):712-716; Wilton et al. 2021. Preprint: doi.org/10.1101/2021.12.03.471180; Vukojicic et al. Cell Rep. 2019;29(10):3087-3100.e7; Howell et al. J Clin Invest. 2011;121(4):1429-44; Williams et al. Mol Neurodegener. 2016;11:26; Jiao et al. Mol Neurodegener. 2018;13(1):45; Lui et al. Cell. 2016 May 5;165(4):921-35; Krukowski et al. Int J Mol Sci. 2018 Nov 26;19(12):3753; Holden et al. Science. 2021;373(6560):eabj2685.

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



Early manifest consistent with patients enrolled in current study

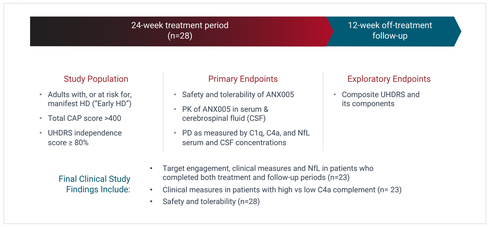
*Higher complement activity in CSF (C4a) of HD patients is associated with disease severity and functional decline.
Presented at HSG, November 2021; Annexon Collaboration with Ed Wild, University College London.
CSF, cerebrospinal fluid; HD, Huntington's disease.

- 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 of manifest HD

Methods/Techniques

- ANX005-HD-01 (NCT04514367) was a multicenter, open-label, phase 2 study testing 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 Demographics Characteristics Were Consistent With Prior HD Natural History Study Cohorts

Study participant characteristics	All patients (N=28)	Treatment completers (N=23)	TRACK-HD* (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)

*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)

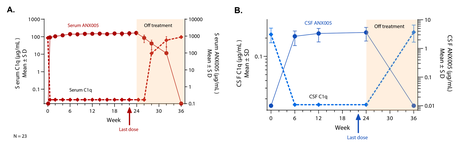
Table 2. ANX005 Was Generally Well-Tolerated

	Safety population (N=28)	
n (%)	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.

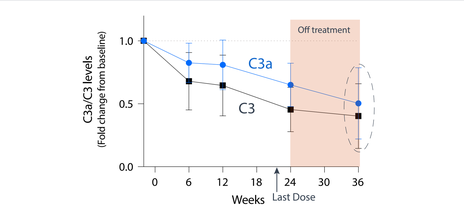
- Steady-state PK were achieved in the serum and CSF by Week 6 (**Figure 4**)

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



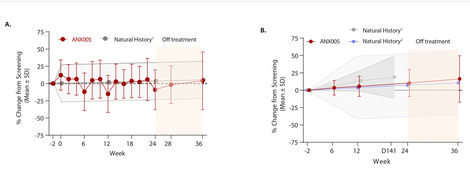
N = 23
CSF, cerebrospinal fluid.

Figure 5. ANX005 Has 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



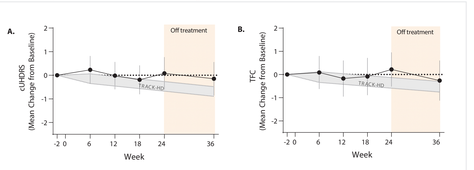
Dashed line represents C4 normal range lower cutoff.
C3 and C3a were measured in the CSF.

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)



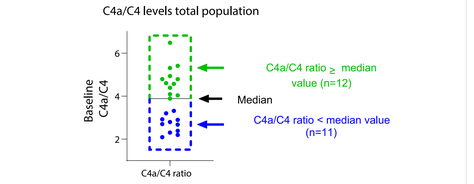
†Interpolated data for manifest cohort; Rodrigues, et al., *Sci Transl Med.* 2020 12 16;12:574)
‡Tabrizi, *NEJM* 2019; 380:2307
CSF, cerebrospinal fluid.

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)



cUHDRS, composite Unified Huntington's Disease Rating Scale; TFC, Total Functional Capacity.
The gray shading represents interpolated natural history from Schobel 2017 (TRACK-HD study).

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



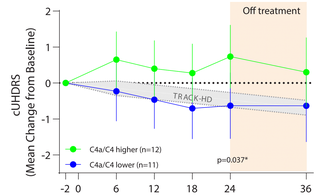
C4a levels divided by levels of C4 (C4a/C4 ratio) to normalize genetic variability in C4 gene copy number.

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)

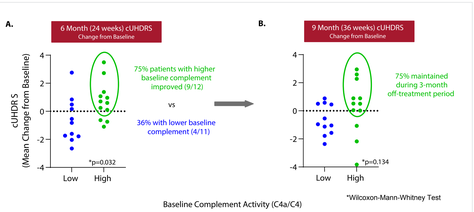
CAG, cytosine-adenine-guanine; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; SWR, Stroop Word Reading; SDMT, Symbol Digit Modalities Test; TFC, Total Functional Capacity; TMS, Total Motor Score.

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



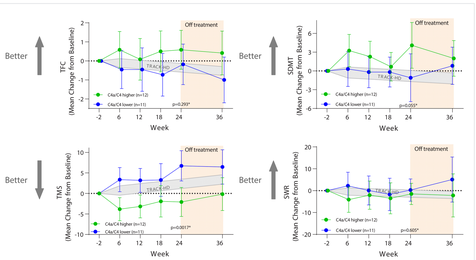
*Nominal p values comparing higher vs lower C4a/C4 groups at Week 2; MMRM; LS means +/- 95% CI; N=23.
The gray shading represents interpolated natural history from Schobel 2017 (TRACK-HD study). The results of the unadjusted and adjusted (for covariates used in TRACK-HD) MMRM analyses were similar.
cUHDRS, composite Unified Huntington's Disease Rating Scale; TFC, Total Functional Capacity.

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)



cUHDRS, composite Unified Huntington's Disease Rating Scale.

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



*MMRM; LS means +/- 95% CI; Comparing higher vs lower groups at week 24.
The gray shading represents interpolated natural history from Schobel 2017 (TRACK-HD study). The results of the unadjusted and adjusted (for covariates used in TRACK-HD) MMRM analyses were similar.
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.

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.

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AM, BH, PL, PC, EC-M, LT, HAK: employment with Annexon Biosciences; equity ownership in Annexon Biosciences.

TY: employment with Annexon Biosciences; equity ownership in Annexon Biosciences; consultancy/advisory role with Biogen and Myelin Repair Foundation.

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