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Huntington's Disease Program Update AMT-130

December 19, 2023

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Opening Remarks

Matt Kapusta
Chief Executive Officer

Huntington's disease (HD): significant unmet medical need

- HD is an inherited, progressive neurodegenerative disease
- 80,000 cases in Europe and North America with many more at risk[1]
- HD strikes relatively young adults and children and progresses relentlessly leading to disability and death
- HD is characterized by disabling motor symptoms including chorea, dystonia, and impaired speech and includes severe cognitive and psychiatric symptoms
- There is a significant impact to families at risk and burden to caregivers
- There are no cures or disease-modifying treatments for HD

Images from Scottish Huntington's Association http://care.hdscotland.org/

1. Medina et al. Movement Disorders, 37, No. 12, (2022)

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AMT-130: ongoing encouraging trends in treated patients

- AMT-130 continues to be generally well-tolerated, with a manageable safety profile across both doses

- Patients treated with AMT-130 show evidence of preserved neurologic function relative to baseline, and potential dose-dependent clinical benefit relative to a non-concurrent criteria-matched natural history

- Continued favorable trends in CSF NfL were observed across both doses, with low-dose patients below baseline at 30 months and high-dose patients near baseline at 18 months

- CSF mHTT values are close to the lower-limit of detection, and may not be an effective measure of target engagement for a striatally-administered HTT-lowering therapy

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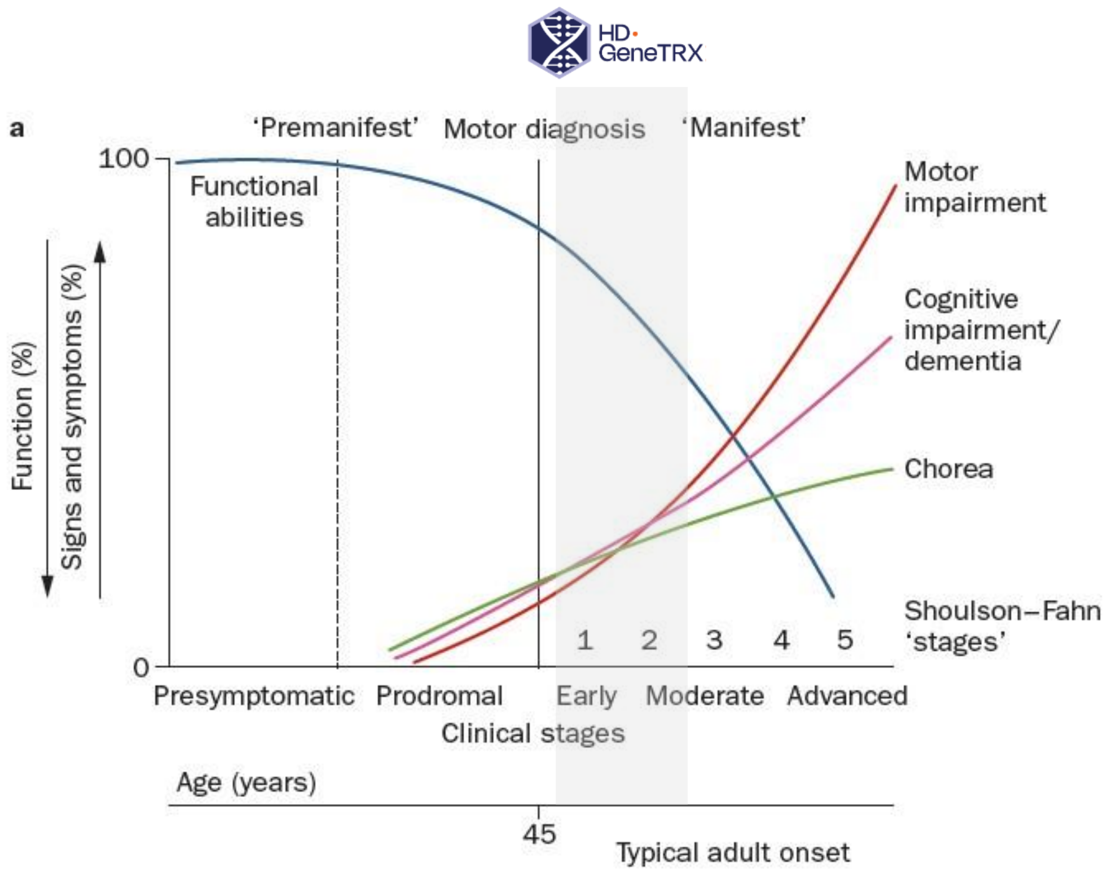
AMT-130 Clinical Trial Overview

Walid Abi-Saab, M.D.
Chief Medical Officer

uniQure Huntington's disease (HD): significant unmet medical need

- Autosomal dominant inherited disorder (50% risk if a parent has HD)
- The disease progresses from premanifest to early motor diagnosis to advanced disease over 10-15 years[1]
- Patients enrolled in the HD-GeneTRX studies are at an early to moderate stage of disease progression



1. Ross, C. A. et al. Nat. Rev. Neurol. 10, 204–216 (2014)

HD-GeneTRX1 - A Phase 1/2, Randomized, Double-Blind, Sham-Control Study to Explore Safety, Tolerability, and Efficacy Signals of Multiple Ascending Doses of Striatally-Administered rAAV5-miHTT Total Huntingtin Gene (HTT) Lowering Therapy (AMT-130) in Early Manifest Huntington's Disease; **HD-GeneTRX2** - Phase Ib/II Study to Explore Safety, Tolerability, and Efficacy Signals of Multiple Ascending Doses of Striatally-Administered rAAV5-miHTT Total Huntingtin Gene (HTT) Lowering Therapy (AMT-130) in Early Manifest Huntington Disease

Huntington's disease (HD): manifestation

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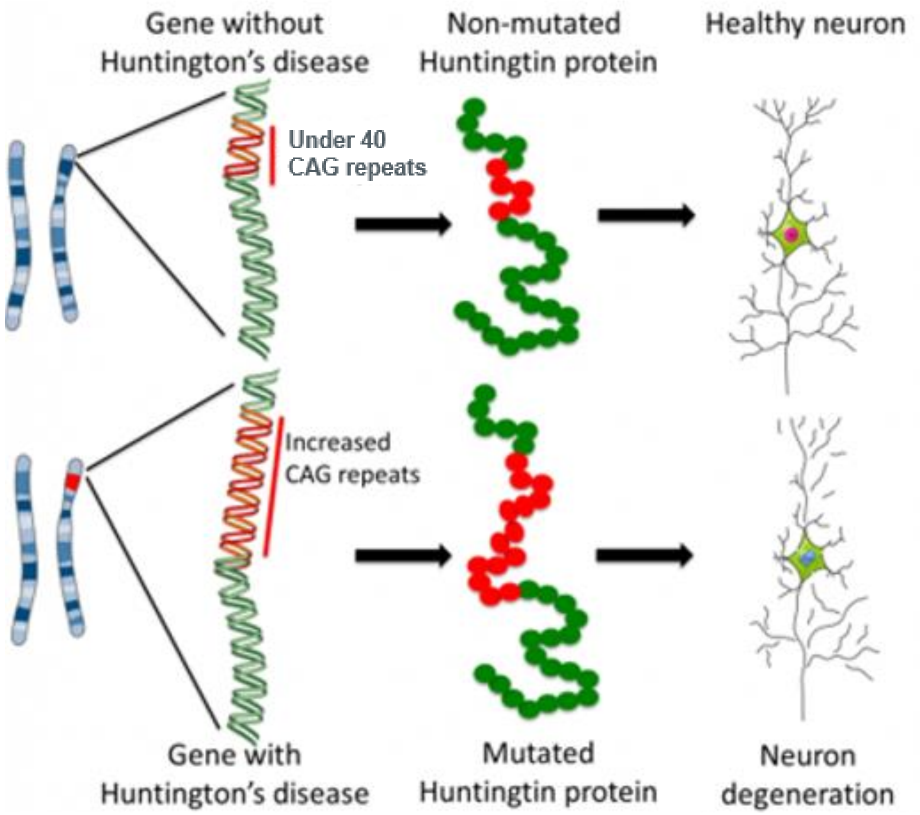
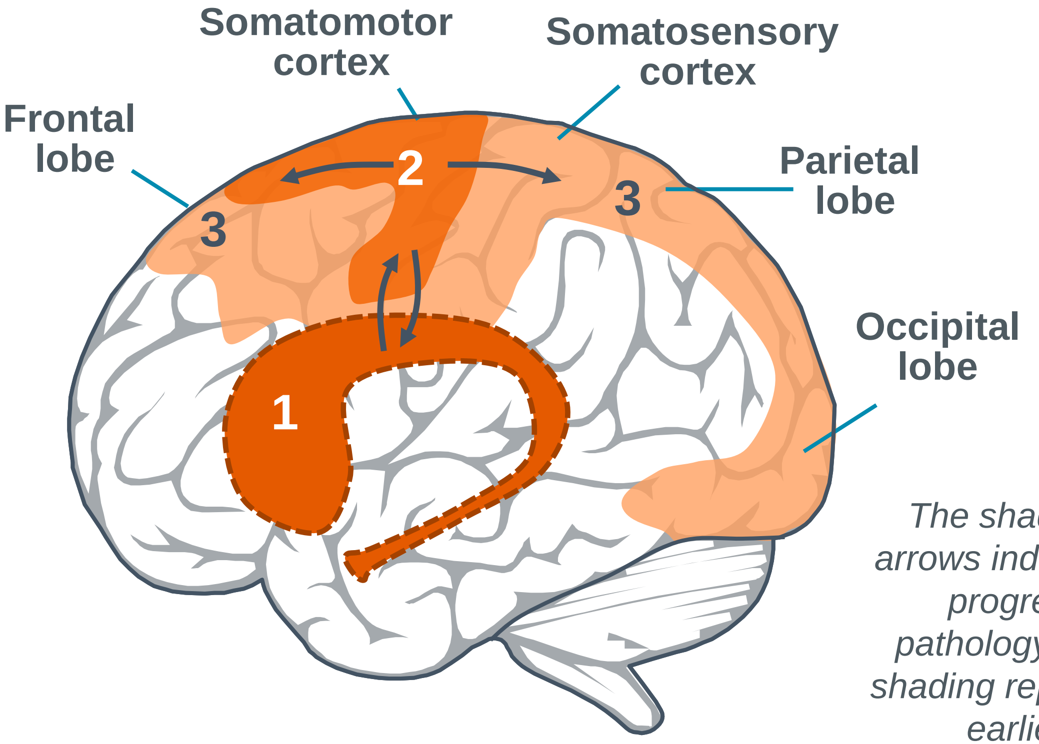
≥ 40 CAG repeat *HTT* DNA → Prolonged CAG repeat HTT1a mRNA → Expanded polyglutamine tract in protein → Protein aggregation → Neuronal degeneration



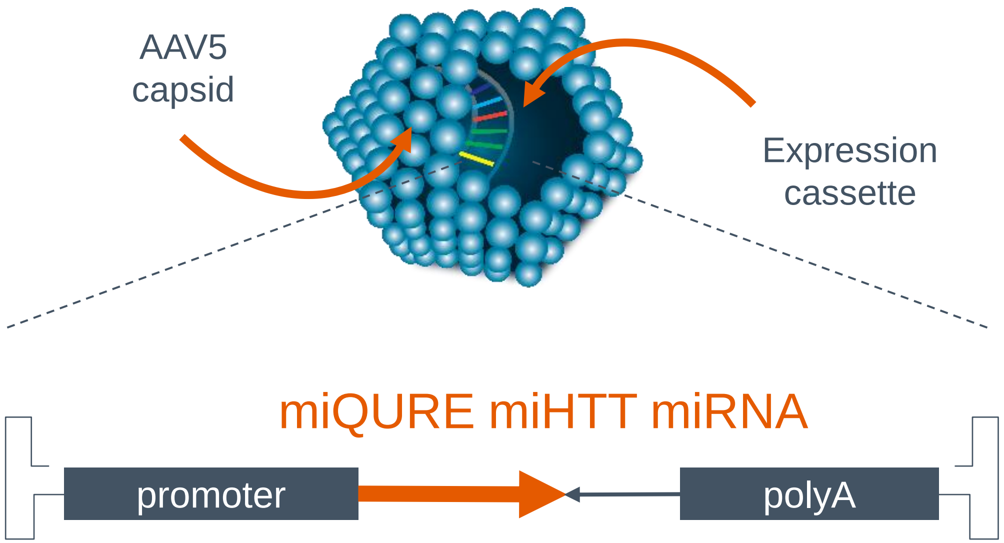


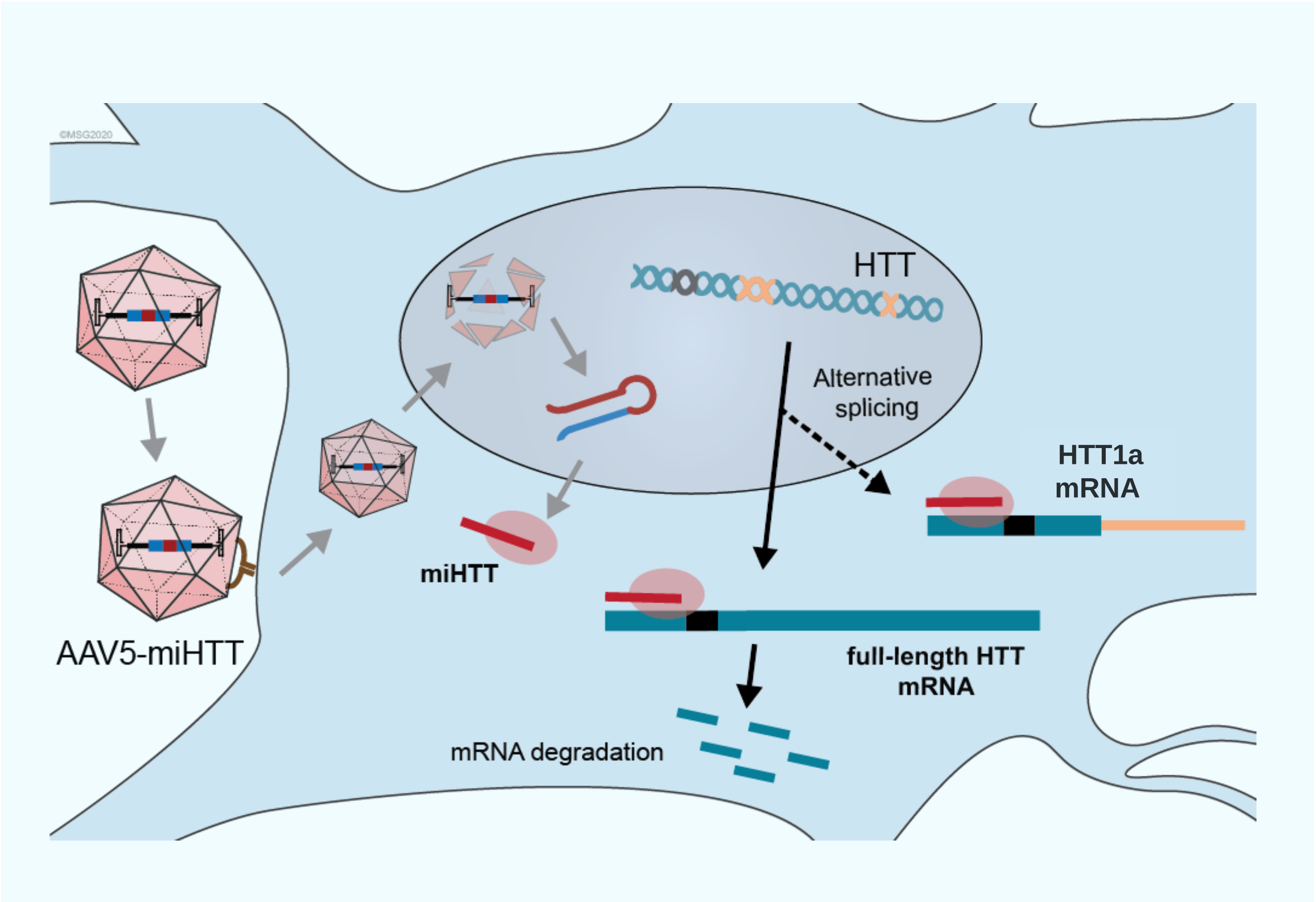
The shading and arrows indicate the progression of pathology. Darker shading represents earlier onset.

Figure adapted from Brundin P, *et al. Nat Rev Mol Cell Biol* 2010;11:301-7.

AMT-130: mechanism of action in Huntington's disease

AMT-130 is a modified AAV5 viral vector containing an HTT exon1 targeting miRNA





AMT-130 is investigational and has not been proven to be safe or effective and is not approved by any regulatory agency.

AMT-130: maximizing potential for clinical impact via direct, intra-striatal convection-enhanced delivery

Three stereotactic injections are delivered on each side into the putamen and caudate nucleus, using convection-enhanced delivery.

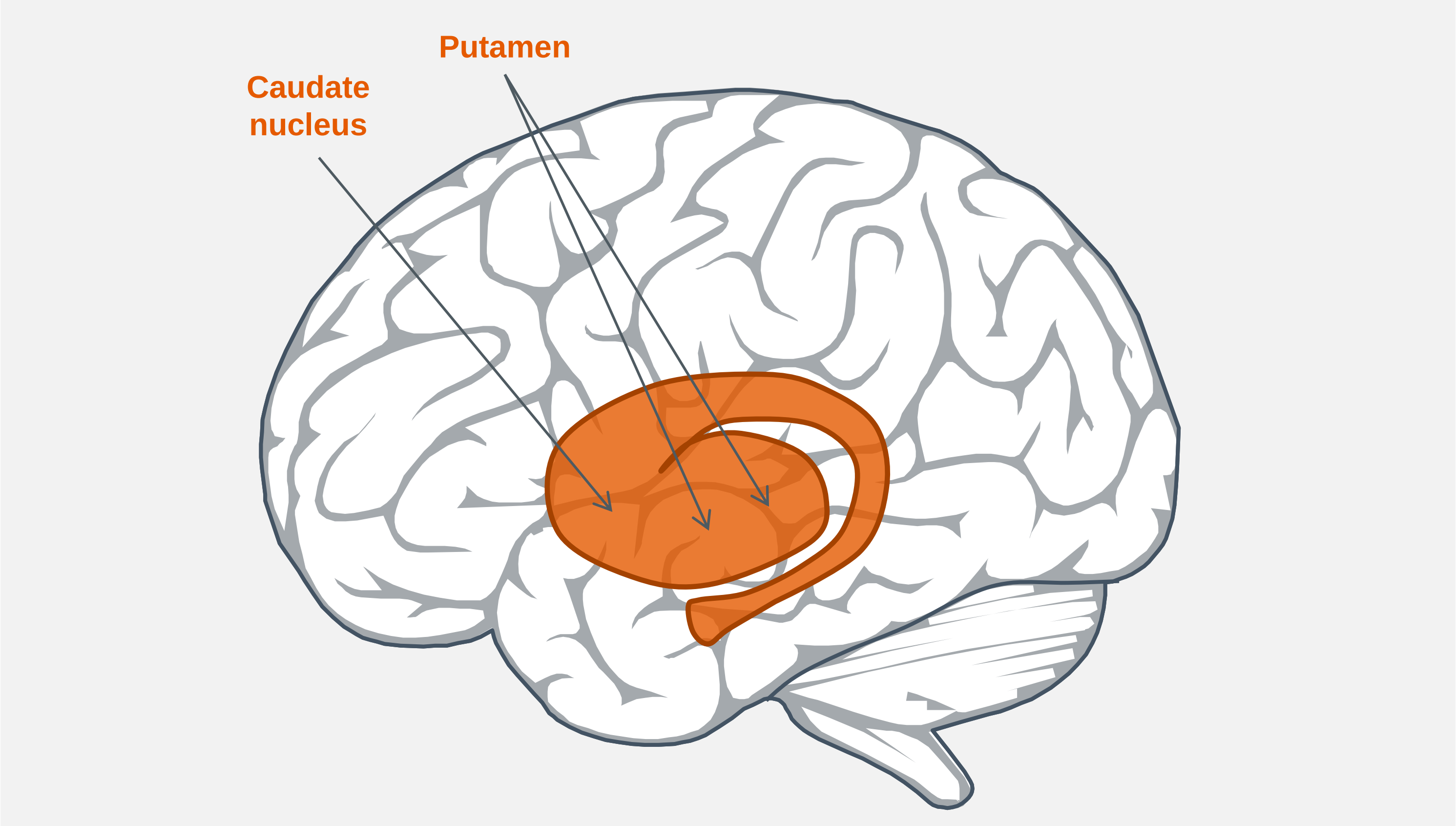


Image reproduced from:
https://www.neuroscientificallychallenged.com/blog/know-your-brain-striatum

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AMT-130: phase I/II U.S. & European clinical trial design

Inclusion Criteria

- ✓ **≥40 CAG**
- ✓ **25 to 65 years of age**
- ✓ **Total functional capacity** (Cohort 1&2, TFC 9-13; Cohort 3, TFC 11-13)
- ✓ **Diagnostic Classification Level (DCL) 4 (motor manifest) or 3 (multidimensional)**
- ✓ **Putamen volume of ≥2.5 cm^3 (per side), and caudate volume of ≥2.0 cm^3 (per side)**
- ✓ **Stable concomitant HD medication for 3 months**

United States, European Cohorts 1 and 2

≤12 weeks

Screening visit

Randomization

Baseline visit

Day 0

Surgery

Post-treatment follow-up 5 years

US: Sham-controlled, blinded follow-up for 12 months, cross-over

EU & UK: Open-label , no sham, same dosing and inclusion criteria

Cross-over of eligible US sham subjects

Long Term Follow-up

Every 3 months through 24 months

Every 6 months years 3-5

Endpoints and Biomarkers

cUHDRS
Total Functional Capacity
Total Motor Score (TMS)
Symbol Digit Modality Test (SDMT)
Stroop Word Reading Test (SWT)

Volumetric MRI

NfL, mHTT

HD·GeneTRX

AMT-130: patient enrollment overview

CT-AMT-130-01 (Phase Ia/II)
double-blind sham-controlled

HD-GeneTRX1

26 Patients

- Low-dose 6e12 AMT-130 (6 Drug, 4 Control)
- High-dose 6e13 AMT-130 (10 Drug, 6 Control)
- Cohort 3

20 patients in HD-GTRX1 have received AMT-130

Four patients in the control arm have crossed over and received AMT-130 (1 low-dose, 3 high-dose)

CT-AMT-130-02 (Phase Ib/II)
open-label

HD-GeneTRX2

13 Patients

- Low-dose 6e12 AMT-130 (6 patients)
- High-dose 6e13 AMT-130 (7 patients)
- Cohort 3

13/13 patients in HD-GTRX2 have received AMT-130

AMT-130: non-concurrent natural history comparator cohorts with and without the minimum striatal volume criteria

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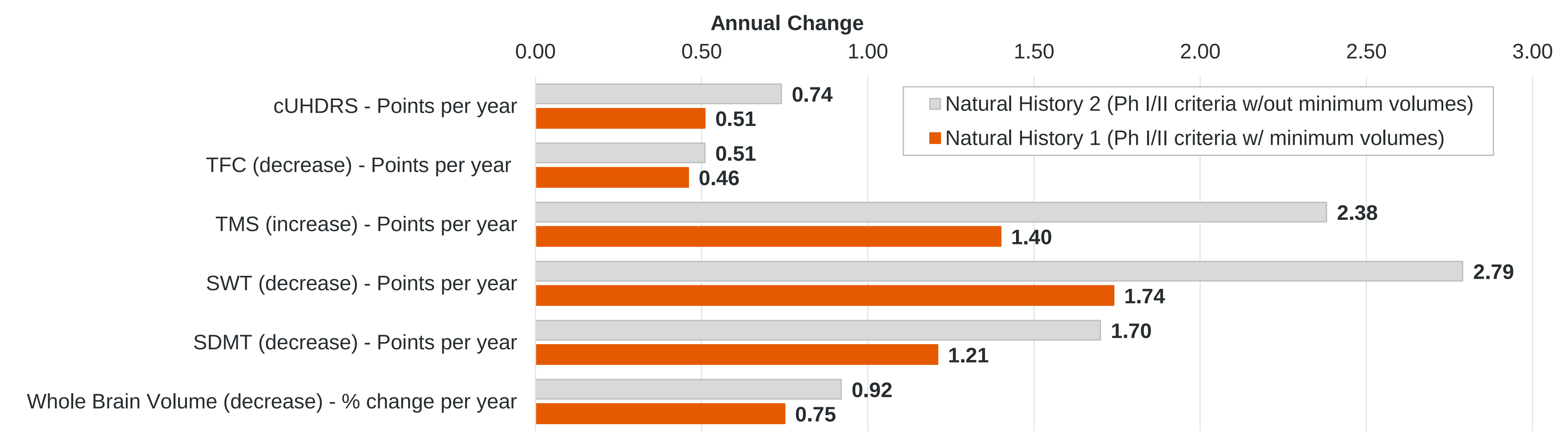
Natural History Cohort 1: subgroup from Natural History cohort 2 that exceed the minimum striatal volumes.

Natural History Cohort 2: TRACK-HD patients that closely match the study's clinical inclusion criteria.



Natural History 1 (Phase I/II inclusion criteria and also exceeds minimum striatal volumes) : N=31; TFC 9-13; DCL 3-4; Putamen volume ≥2.5cm^3; Caudate volume ≥2.0cm^3 per side

Natural History 2 (Phase I/II inclusion criteria without minimum striatal volume) : N=105; TFC 9-13; DCL 3-4

AMT-130: baseline demographic and disease characteristics generally balanced across all groups

Characteristic (mean, SD, range as applicable)	Control n = 10	AMT-130 Low-dose n = 12	AMT-130 High-dose n = 17
Males/Females (n)	6/4	8/4	8/9
Age at screening	47.0 (8.3), 34 - 58	44.1 (10.3), 25 - 57	45.8 (8.7), 33 - 65
Time since initial diagnosis (yrs)	2.1 (3.5), 0 - 9	1.6 (1.8), 0 – 5.3	2.4 (3.0), 0 - 10
Cytosine-Adenine-Guanine (CAG) repeats	42.8 (1.3), 40 - 45	43.5 (3.1), 40 - 51	42.0 (1.7), 40 - 46
CAG-Age-Product (CAP) score	423.2 (62.7), 317.6 - 541.7	408.3 (55.4), 316.9 – 486.0	377.0 (80.0), 221.9 – 506.7
Total Functional Capacity (TFC)	12.0 (1.2), 10 - 13	11.9 (0.9), 11 - 13	12.2 (1.3), 9 - 13
Total Motor Score (TMS)	12.3 (5.0), 5 - 19	13.3 (5.6), 6 - 23	12.1 (5.9), 5 - 26
Composite UHDRS (cUHDRS)	15.1 (1.47), 11.8 - 16.9	14.1 (2.26), 11.0 - 18.3	14.9 (2.21), 10.9 - 19.6
Disease confidence level DCL 3 /4 (n)	4/6	3/9	6/11
Prognostic index (PIN) score	0.95 (0.59), 0.19 – 1.69	1.03 (0.69), 0.02 – 1.85	0.77 (0.85), -0.62 – 2.24

Safety and Tolerability

AMT-130 Phase I/II U.S. and European Clinical Trials

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AMT-130: safety and tolerability

- AMT-130 was generally well-tolerated across both dose cohorts
- Surgical and drug-related adverse events were manageable
  - CNS inflammation, seen in several SAEs, improved with glucocorticoid medication; a short course of perioperative steroid prophylaxis has been added to the treatment regimen for Cohort 3
- There were no clinically relevant differences between treatment groups in vital signs, ECG, or clinical chemistry and hematology laboratory values

AMT-130: safety and tolerability

	Control (n=10)		Low-dose AMT-130 (n=13)		High-dose AMT-130 (n=20)	
	N	(%)	N	(%)	N	(%)
Any TEAEs	10	100.0	12	92.3	20	100.0
Any SAEs (peri-operative)	1	10.0	2	15.4	5	25.0
Any Drug-Related TEAE	0	0.0	0	0.0	6	30.0
Any Drug-Related SAE	0	0.0	0	0.0	4	20.0
CNS Inflammation					4 *	20.0
Most Common TEAEs (≥30% in at least one group)						
Procedural headache	5	50.0	4	30.8	9	45.0
Headache	3	30.0	3	23.1	9	45.0
Post lumbar puncture syndrome	6	60.0	2	15.4	7	35.0
Procedural complication	4	40.0	4	30.8	5	25.0
Procedural pain	5	50.0	2	15.4	6	30.0
Upper respiratory tract infection	1	10.0	4	30.8	0	0.0

** One SAE reported as "tension headache" was retrospectively recognized by uniQure as a case of CNS inflammation.*

AE, adverse event; N, number of patients; TEAE, treatment-emergent adverse event; SAE, serious adverse event. TEAEs are defined as AEs after Day 0. Perioperative AEs had onset Day 0 to 13.

Data cut-off as of September 30, 2023

Exploratory Efficacy Data

AMT-130 Phase I/II U.S. and European Clinical Trials

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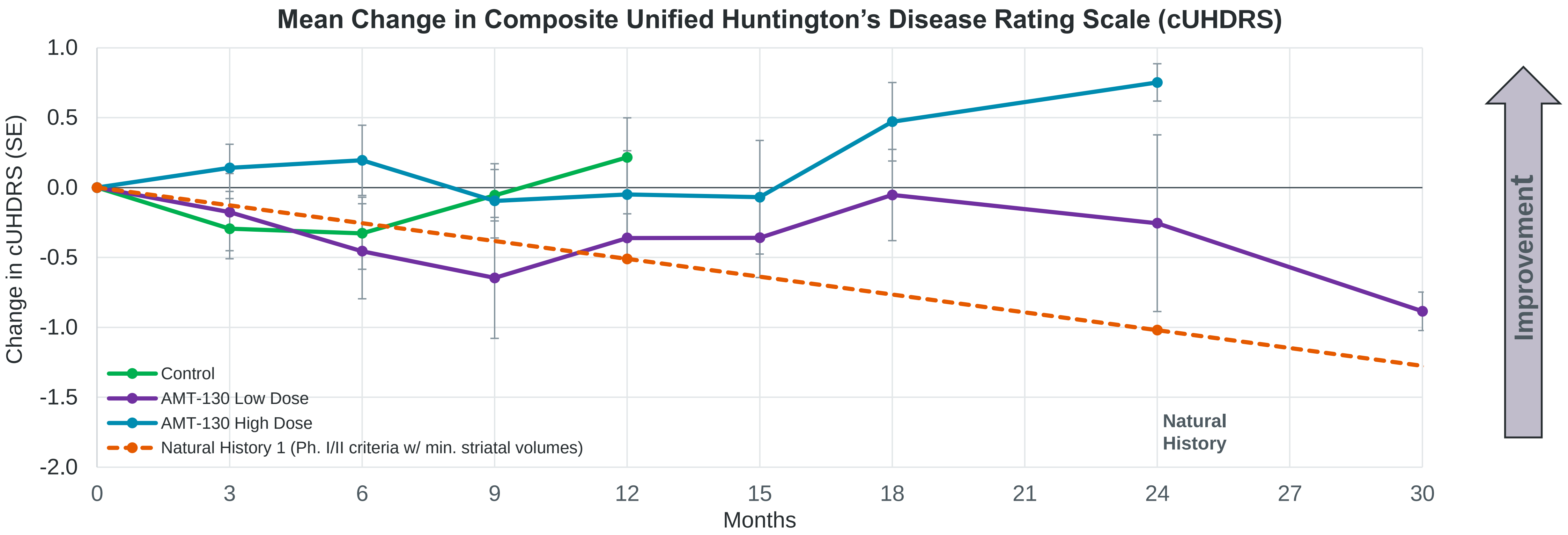
AMT-130: cUHDRS remained favorable in treated patients compared to natural history; high-dose patients preserved cUHDRS relative to baseline



Patients	Base	3M	6M	9M	12M	15M	18M		24M		30M
Low Dose	12	12	12	12	12	12	12		6		5
High Dose	17	17	14	14	14	13	9		2		
Control	10	9	10	10	9						

cUHDRS is a composite endpoint developed to evaluate disease progression in early-to-moderate manifest HD. The scoring algorithm combines four elements: Total Functional Capacity (TFC), Total Motor Score (TMS), Symbol Digit Modalities Test (SDMT) and Stroop Word Reading Test (SWT)

HD GeneTRX

Standard Error (SE); TRACK HD (Poster CHDI 2022)

AMT-130: treated patients showed a favorable difference in TFC when compared to natural history and stabilization relative to baseline

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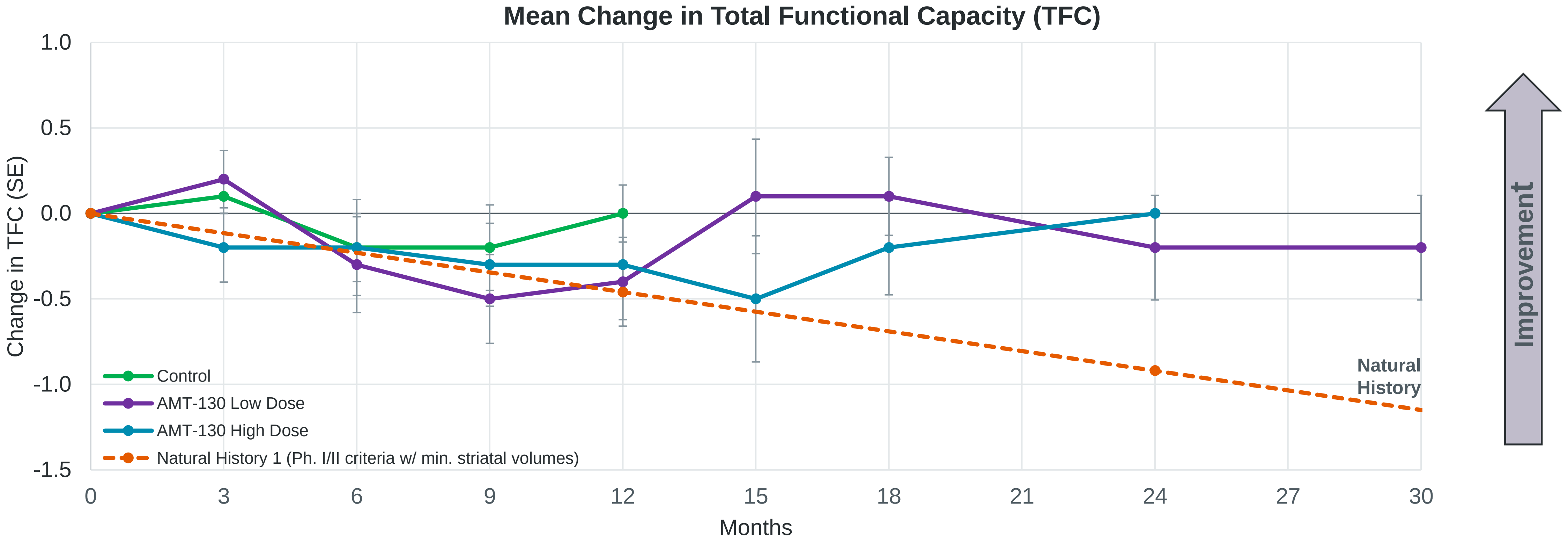

Patients	Base	3M	6M	9M	12M	15M	18M		24M		30M
Low Dose	12	12	12	12	12	12	12		6		6
High Dose	17	17	14	14	14	13	9		2		
Control	10	10	10	10	9						

TFC measures functional abilities in five categories, including occupation, finances, domestic chores, activities of daily living, and care level. Each category is rated on a scale, with higher scores indicating better functioning. The total TFC score ranges from 0 to 13, with lower scores representing greater functional impairment.

Standard Error (SE); TRACK HD (Poster CHDI 2022)

HD GeneTRX

AMT-130: treated patients showed a favorable difference in TMS when compared to natural history and stabilization relative to baseline

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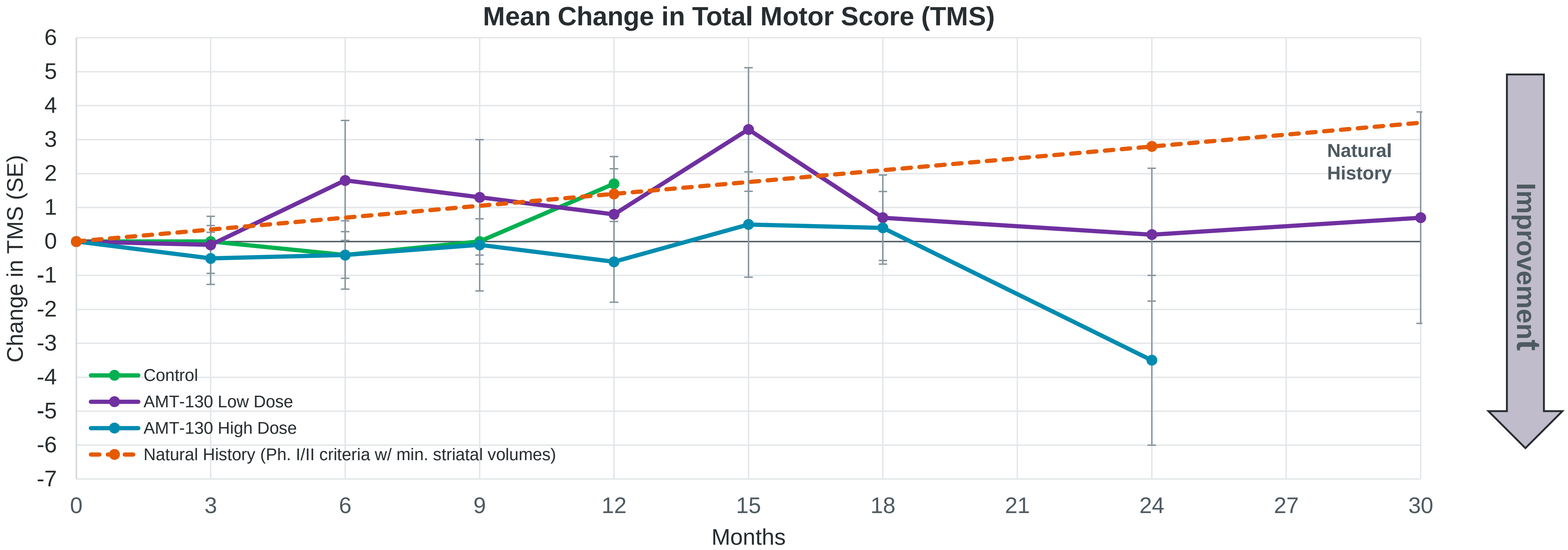

Patients	Base	3M	6M	9M	12M	15M	18M		24M		30M
Low Dose	12	12	12	12	12	12	12		6		6
High Dose	17	17	14	14	14	13	9		2		
Control	10	10	10	10	9						

TMS evaluates the patient's motor function, focusing on involuntary movements (chorea, dystonia), voluntary movements, eye movements, and muscle tone (rigidity). It consists of 31 items, each rated on a 0-4 scale, with higher scores indicating more severe motor impairment. The total motor score ranges from 0 to 124.

HD-GeneTRX

Standard Error (SE); TRACK HD (Poster CHDI 2022)

AMT-130: high-dose treated patients preserved function in SWT relative to baseline

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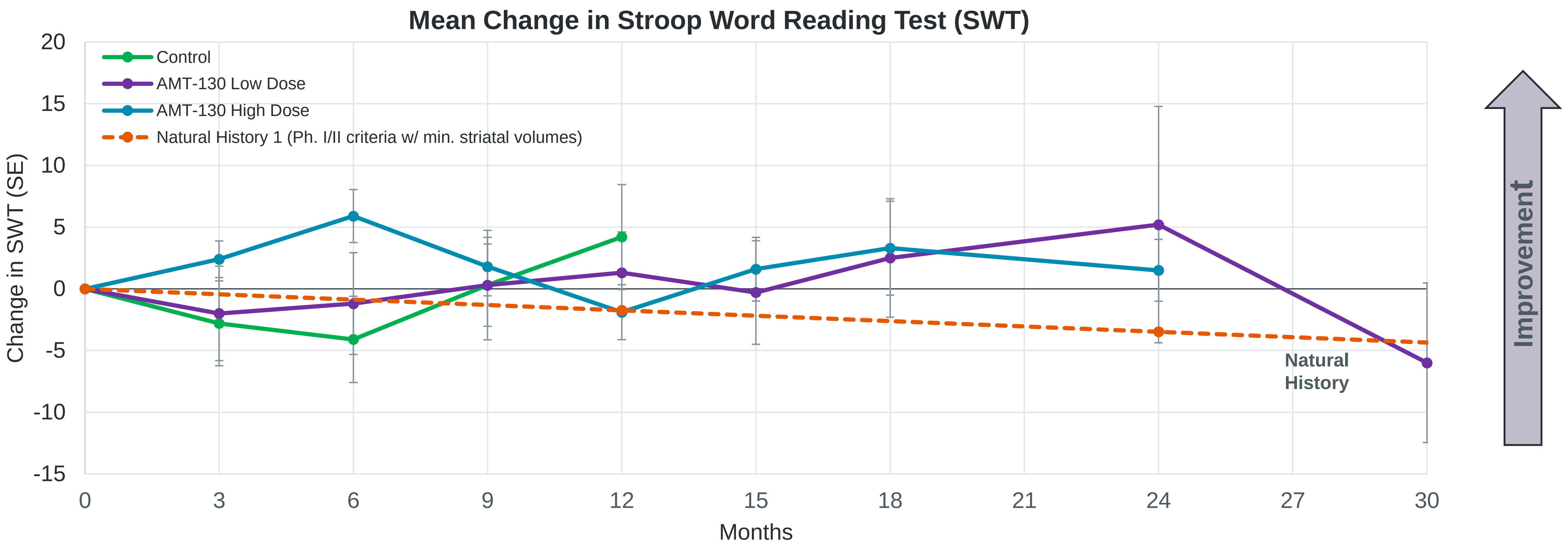


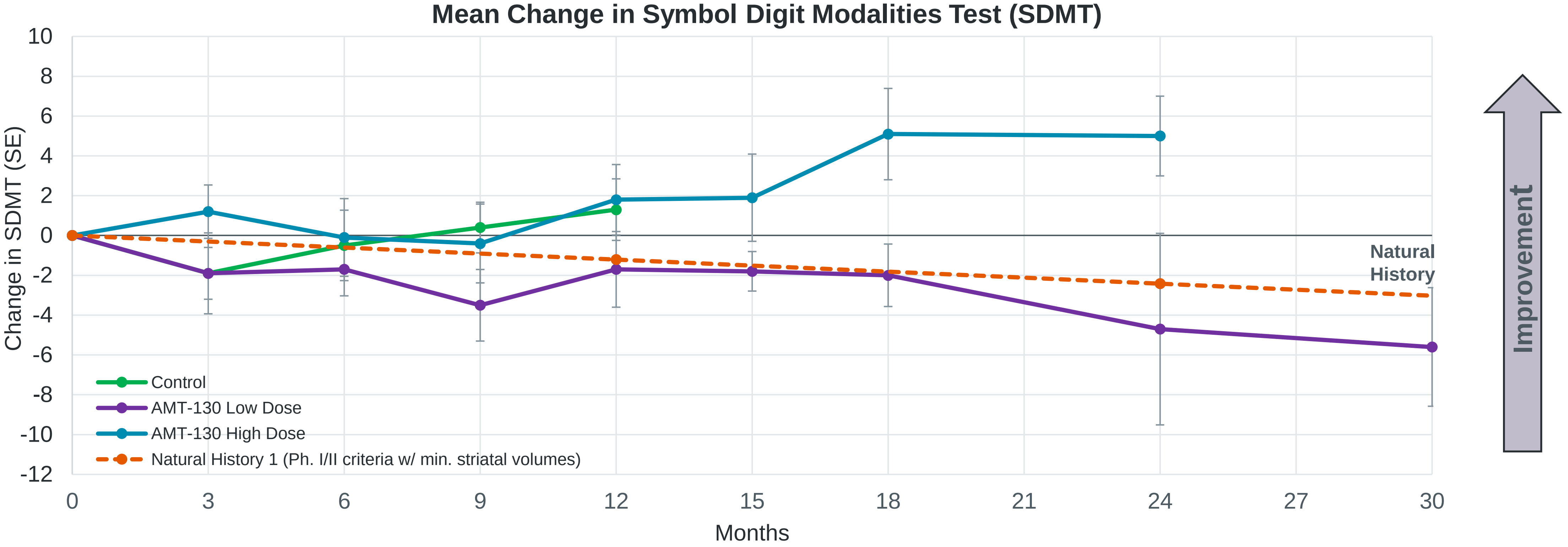
Patients	Base	3M	6M	9M	12M	15M	18M		24M		30M
Low Dose	12	12	12	12	12	12	12		6		6
High Dose	17	17	14	14	14	13	9		2		
Control	10	9	10	10	9						

SWT is scored by measuring the time it takes for an individual to correctly name the ink color of a series of words. The score used to assess performance is typically the difference in time between the word-reading condition and the color-word naming condition (i.e., the interference effect).

HD GeneTRX

Standard Error (SE); TRACK HD (Poster CHDI 2022)

AMT-130: high-dose treated patients preserved baseline with favorable trends to natural history in SDMT



Patients	Base	3M	6M	9M	12M	15M	18M		24M		30M
Low Dose	12	12	12	12	12	12	12		6		5
High Dose	17	17	14	14	14	13	9				
Control	10	10	10	10	9						

SDMT evaluates processing speed, attention, and working memory. Range (0-110) Mean in young adults = 49 +/- 13

Standard Error (SE); TRACK HD (Poster CHDI 2022)

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AMT-130: clinical and functional data findings

- Data at this interim time point suggest a potentially positive clinical effect of AMT-130 on disease progression
- After 30 months, low-dose AMT-130 preserved motor function and functional capacity relative to baseline and relative to the natural history
- After 18 months, high-dose AMT-130 preserved diverse functions relative to baseline and trends favorably to the natural history across all functional measures
- Through its 12-month follow-up, the control group experienced worsening of the Total Motor Score in line with the natural history, but preserved function on other clinical measures

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Biomarker & Volumetric Imaging Data

AMT-130 Phase I/II U.S. and European Clinical Trials

AMT-130: CSF NfL continued favorable trends; low-dose below baseline at month 30 with high-dose near baseline at month 18

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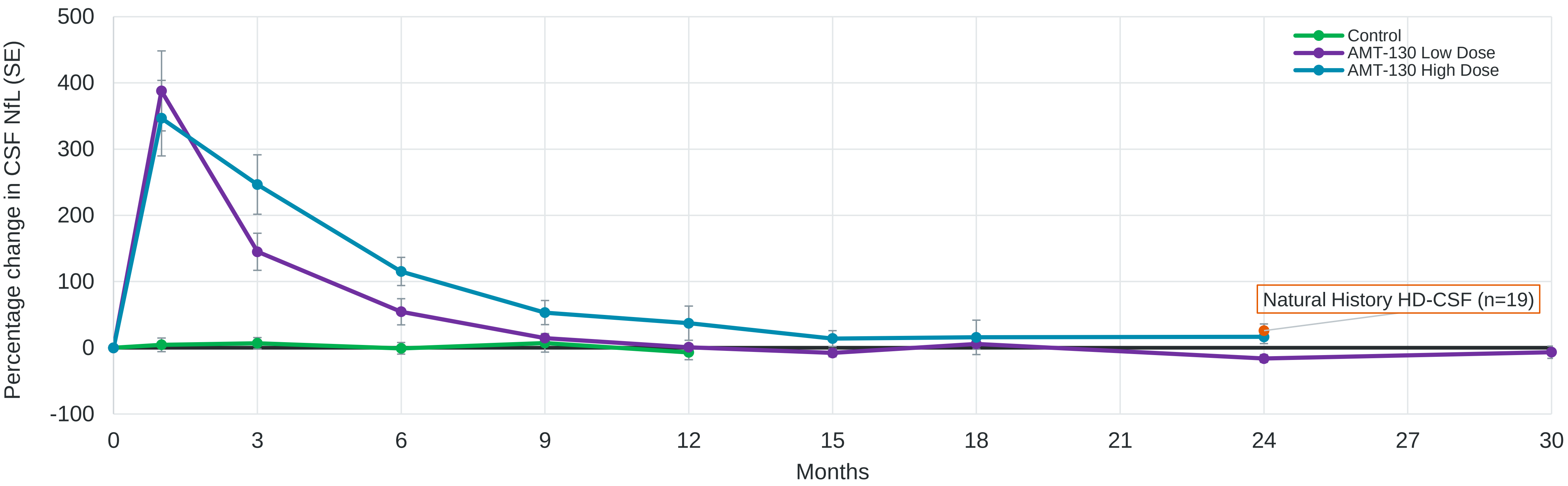
CSF NfL percentage change from baseline



Patients	Base	1M	3M	6M	9M	12M	15M	18M		24M		30M
Low-Dose	12	12	11	12	12	12	12	12		6		6
High-Dose	17	17	16	13	13	11	11	9		2		
Control	10	9	9	9	7	7						

HD·GeneTRX

CSF, Cerebrospinal fluid; NfL Neurofilament light chain; Standard Error (SE)

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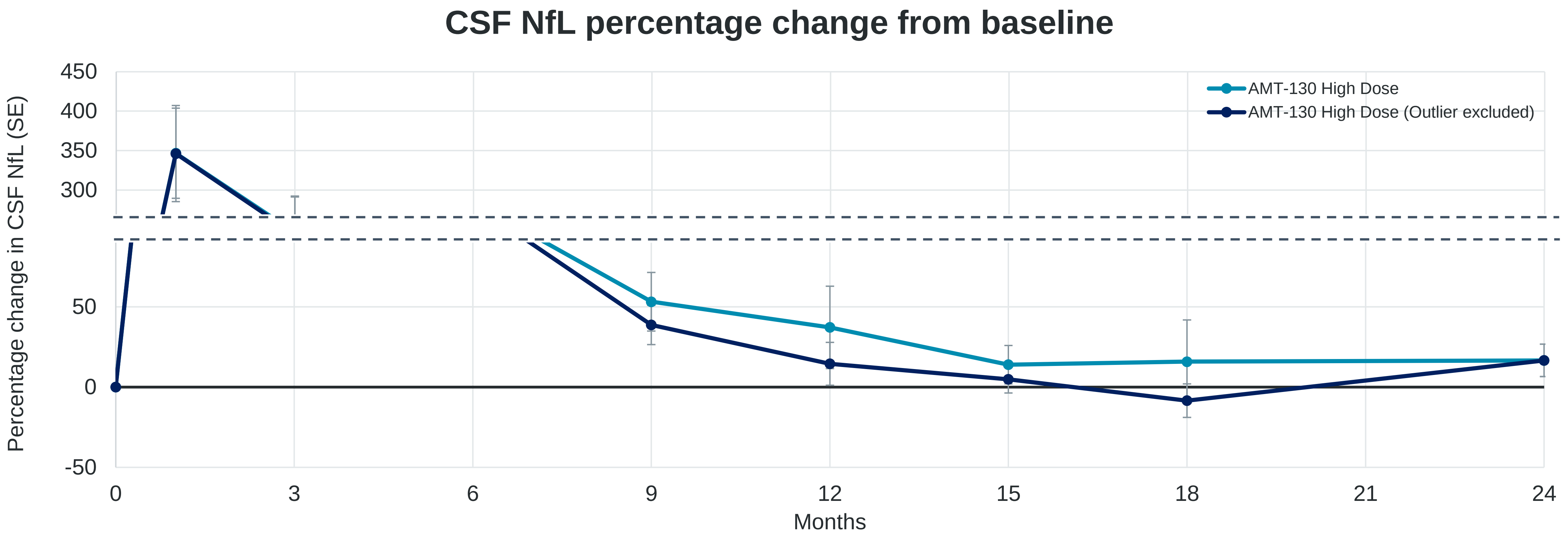
AMT-130: excluding single high-dose outlier*, CSF NfL trended below baseline at month 18 with tighter error bars



Patients	Base	1M	3M	6M	9M	12M	15M	18M		24M
High-Dose	17	17	16	13	13	11	11	9		2
High-Dose (Outlier excluded)	16	16	15	12	12	10	10	8		2

* Single patient experienced a late-onset serious adverse event of central nervous system inflammation around Month 12 with CSF NfL levels approximately 2 to 3-fold higher relative to baseline until their last measurement at Month 18

HD·GeneTRX

CSF, Cerebrospinal fluid; NfL Neurofilament light chain; Standard Error (SE)

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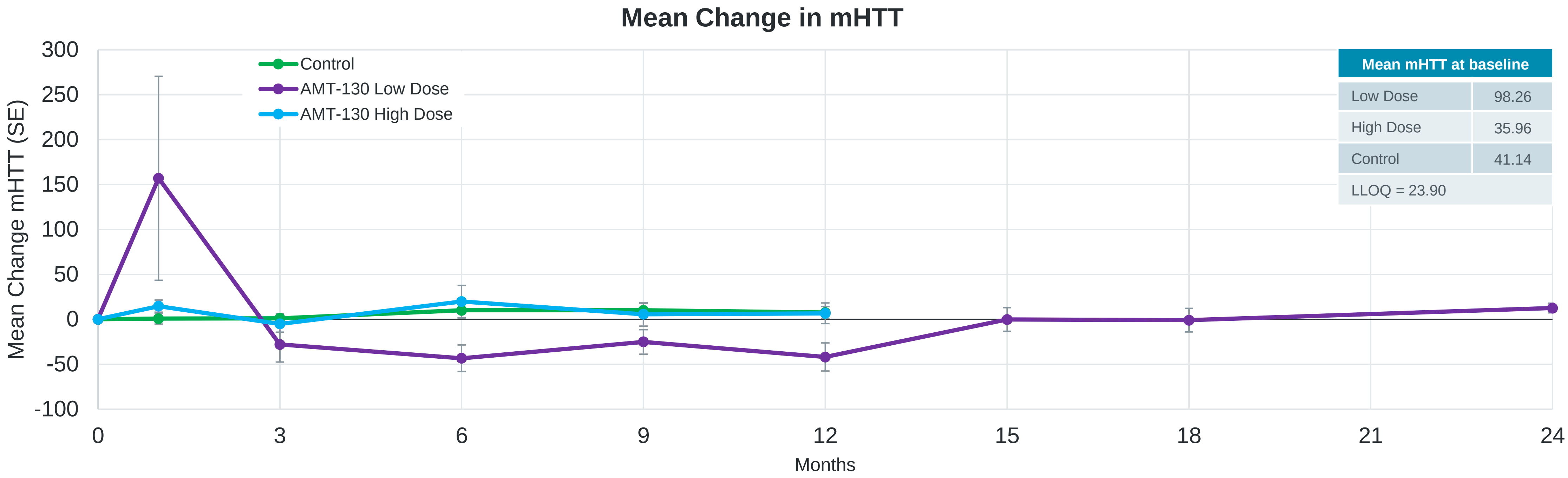
AMT-130: mean CSF mHTT consistent with previous data, likely not reflective of pharmacodynamic effects in targeted brain regions



Mean mHTT at baseline	
Low Dose	98.26
High Dose	35.96
Control	41.14
LLOQ = 23.90	

Patients	Base	1M	3M	6M	9M	12M	15M	18M		24M
Low Dose	11	11	10	11	11	11	5	5		5
High Dose	11	11	11	9	10	9				
Control	8	8	8	8	7	5				

Note: CSF samples were analyzed to quantify the level of mHTT using a different assay than was used to generate data shared publicly in June 2023. CSF samples are now batched. As a result, individual subject and sample results generated with batching may differ from those obtained previously.

HD· GeneTRX

Standard Error (SE); Lower limit of quantification (LLOQ)

AMT-130: changes in total brain volume may be confounded by surgical procedure and do not appear to be clinically meaningful

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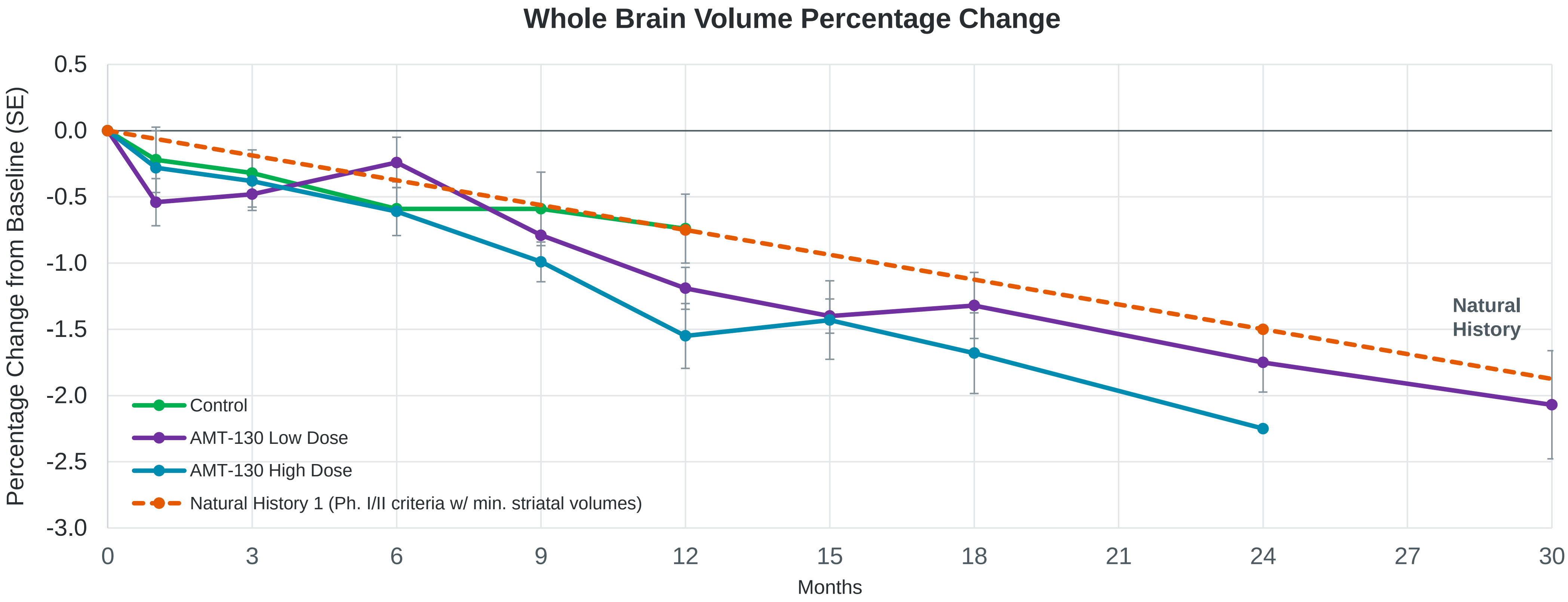

Patients	Base	1M	3M	6M	9M	12M	15M	18M		24M		30M
Low Dose	12	10	10	11	12	12	12	12		6		6
High Dose	17	16	17	14	14	14	13	9		2		
Control	10	10	10	10	10	9						

HD GeneTRX

Standard Error (SE)

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Conclusions

AMT-130 Phase I/II U.S. and European Clinical Trials

AMT-130: promising trends in clinical assessments and CSF NfL support continuing development

- AMT-130 was generally well-tolerated, with a manageable safety profile; SAE cases of CNS inflammation have clinically responded to glucocorticoids
- Patients treated with both doses of AMT-130 show evidence of preserved neurologic function relative to baseline, and potential clinical benefit relative to a non-concurrent natural history
- CSF NfL trends are favorable following the post treatment spike with the low-dose crossing baseline at approximately 12 months with relative stability through month 30, and the high-dose near baseline at month 18
- Brain volumetric changes do not appear to be clinically meaningful in light of the surgical intervention and promising clinical and biomarker data
- CSF mHTT values are close to the lower-limit of quantification, and may not be an effective measure of target engagement for a striatally-administered HTT-lowering therapy

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AMT-130 Clinical Program Next Steps

AMT-130 Phase I/II U.S. and European Clinical Trials

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AMT-130: next steps in clinical development

- Q4 2023: Initiated Cohort 3 in Phase I/II trials in the U.S. and Europe to investigate the effects of immune suppression on perioperative safety
- Q1 2024: Request regulatory interactions to discuss the U.S. and European data and potential regulatory strategies for ongoing development
- Mid 2024: Clinical update on Phase I/II trials out to three years in the US study and two years in the European study

Key Opinion Leader Perspective

Edward Wild, Ph.D., FRCP
University College London

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Research Analyst Questions

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Closing Remarks

Matt Kapusta
Chief Executive Officer

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