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Huntington's Disease Program Update AMT-130

June 21, 2023

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Forward-looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as “anticipate,” “believe,” “could,” “estimate,” “expect,” “goal,” “intend,” “look forward to,” “may,” “plan,” “potential,” “predict,” “project,” “should,” "will,” “would” and similar expressions and the negatives of those terms. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this presentation. These forward-looking statements include, but are not limited to, the potential clinical and functional effects of AMT-130, the expected completion of enrollment in our European, open-label Phase Ib/II study of AMT-130, the initiation of a third cohort in our ongoing U.S. Phase I/II clinical trial and the timing and release of our clinical data. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, risks related to conducting the clinical trial for Huntington’s disease, the impact of financial and geopolitical events on us and the wider economy and health care system, our clinical development activities, clinical results, collaboration arrangements, regulatory oversight, product commercialization and intellectual property claims, as well as the risks, uncertainties and other factors described under the heading “Risk Factors” in our periodic securities filings, including our Annual Report on Form 10-K filed with the SEC on February 27, 2023 and our Quarterly Report on Form 10-Q filed with the SEC on May 9, 2023. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future.

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Opening Remarks

Matt Kapusta
Chief Executive Officer

uniQure 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 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

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

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

AMT-130: key takeaways on the interim analysis

Promising data show early trends of a positive impact on disease progression and support continued development of AMT-130

1. AMT-130 was generally well-tolerated with a manageable safety profile

2. Patients treated with both doses of AMT-130 show early evidence of preserved function relative to baseline and clinical benefit relative to natural history

3. CSF NfL was below baseline and natural history at 24 months in low-dose patients and is declining towards baseline in high-dose patients at 12 months

4. Suppression of CSF mHTT in low-dose cohort supports AMT-130 target engagement; greater variability observed in high-dose cohort

AMT-130: next steps in clinical development

- Q3 2023: Completion of enrollment in Phase I/II trial in EU/UK
- 2H 2023: Initiation of Cohort 3 in Phase I/II trial in the U.S. to investigate the effects of immunosuppression on perioperative safety
- Q4 2023: Clinical update on Phase I/II trial including additional 18- and 30-month data on US cohorts and 12-month follow-up on low-dose cohort from EU/UK study
- Q1 2024: Meeting with regulators to discuss data and potential path forward for clinical development

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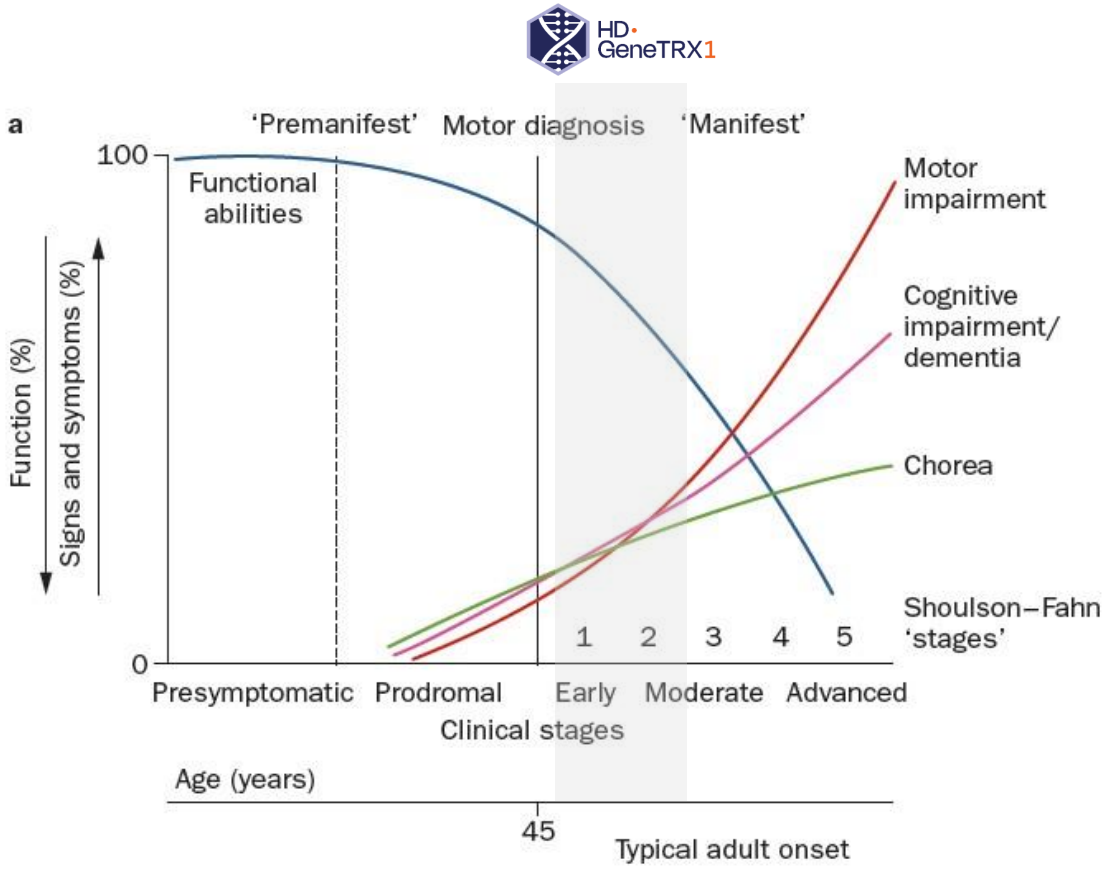
AMT-130 Clinical Trial Overview

Ricardo Dolmetsch, Ph.D.
President of Research and Development

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

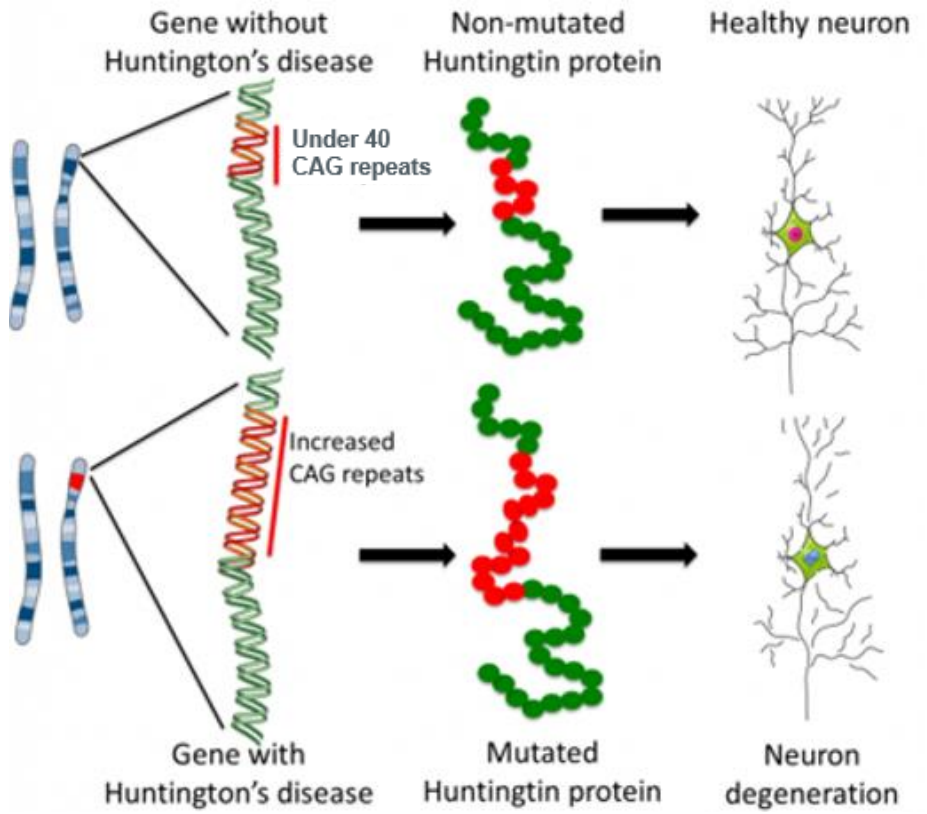
- Autosomal dominant inherited disorder (50% risk if your parent has HD)
- The disease progresses from premanifest to early motor diagnosis to advanced disease over 10-15 years[1]
- Patients enrolled in the HD-TRX1 study are at an early to moderate stage of disease progression (Shoulson-Fahn stage 1, HD-ISS stage 2-3)

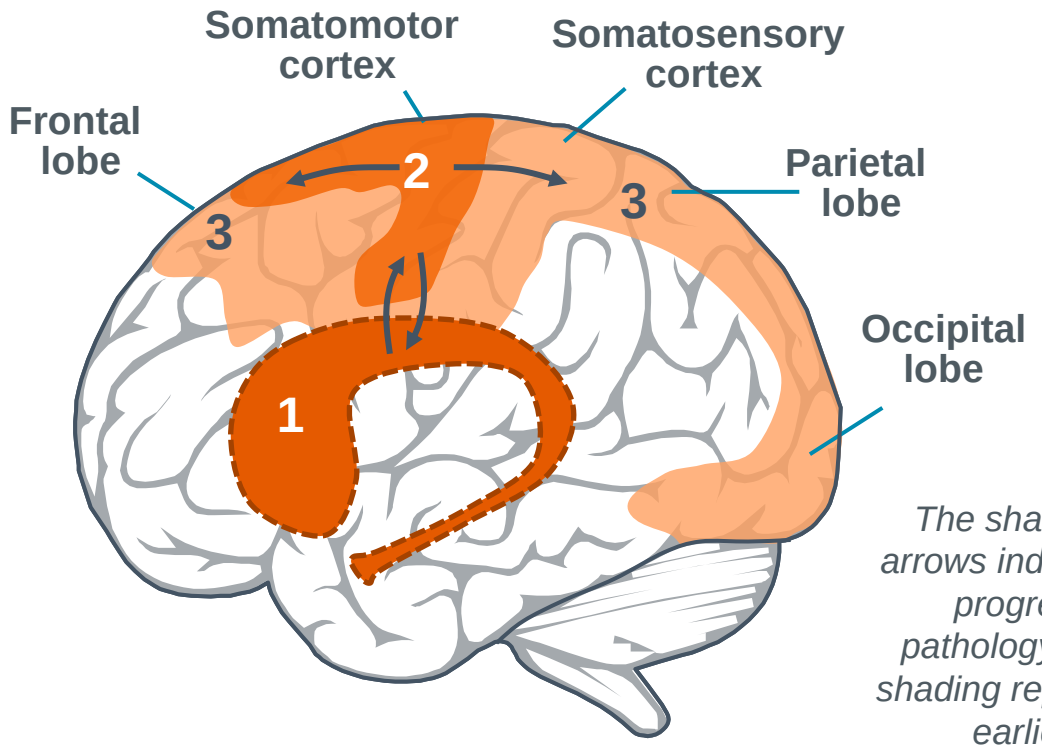


1. Ross, C. A. et al. Nat. Rev. Neurol. 10, 204–216 (2014)

uniQure Huntington's disease (HD): manifestation

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



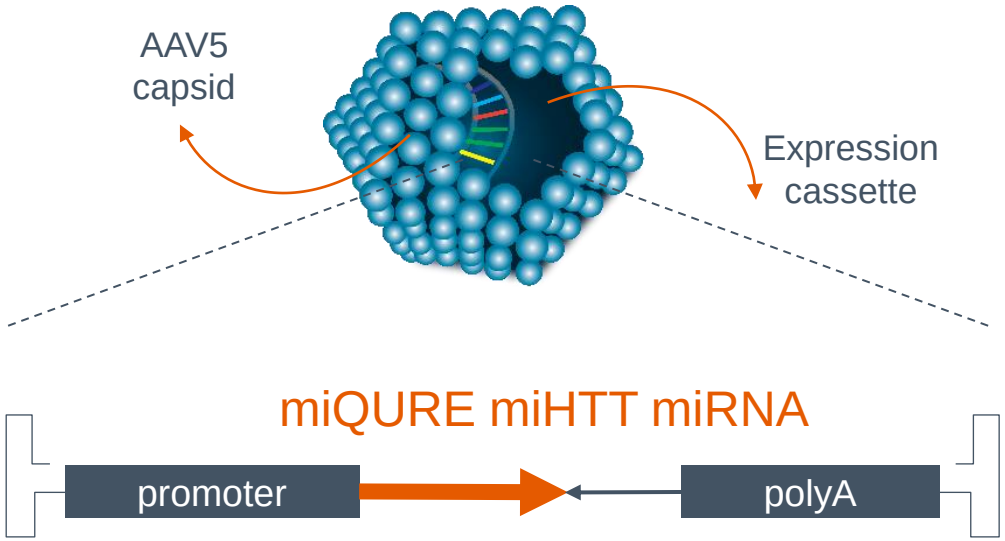


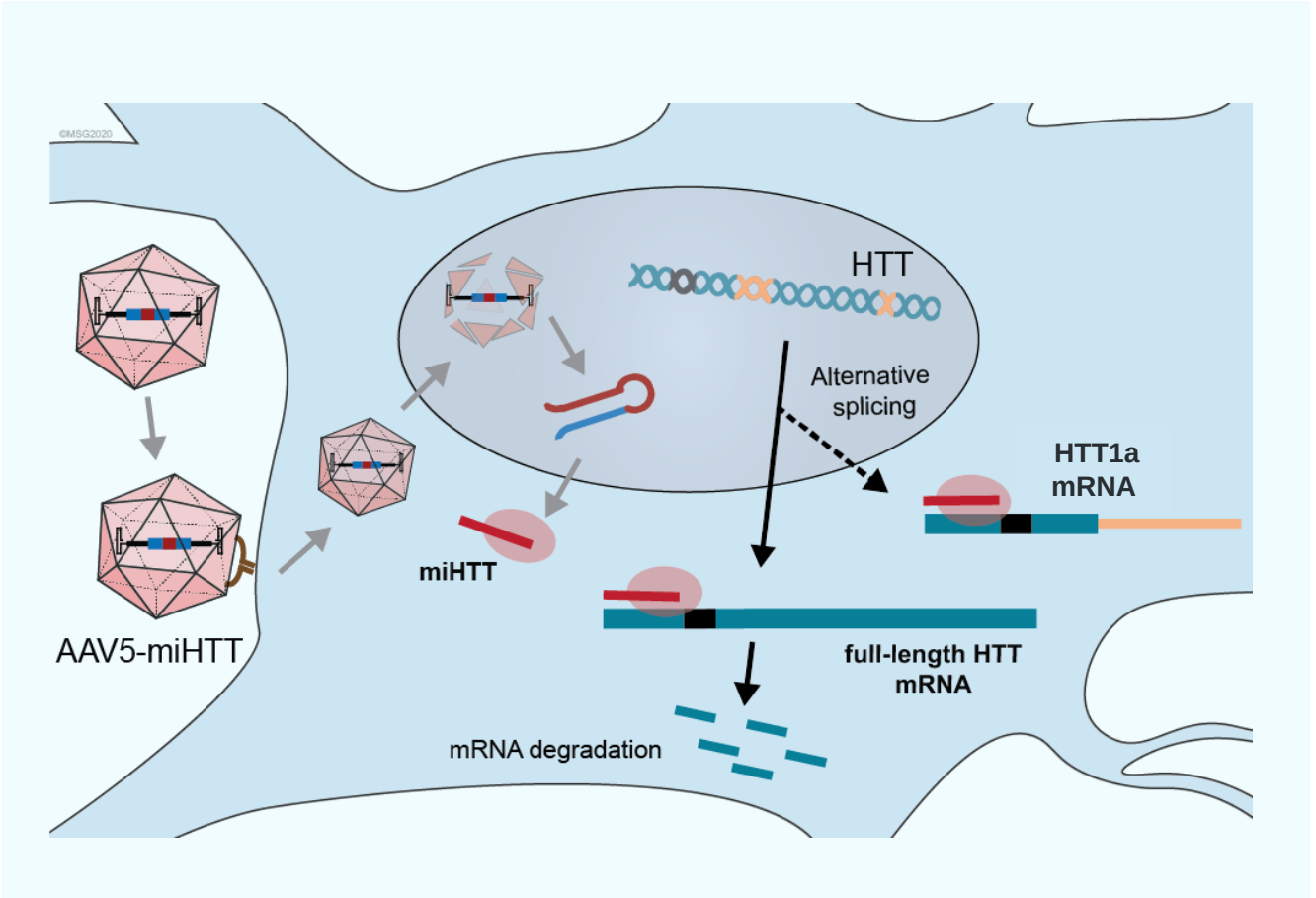
The shading and arrows indicate the progression of pathology. Darker shading represents earlier onset.

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

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Three stereotactic injections delivered on each side into the putamen and caudate nucleus, using convection enhancement.

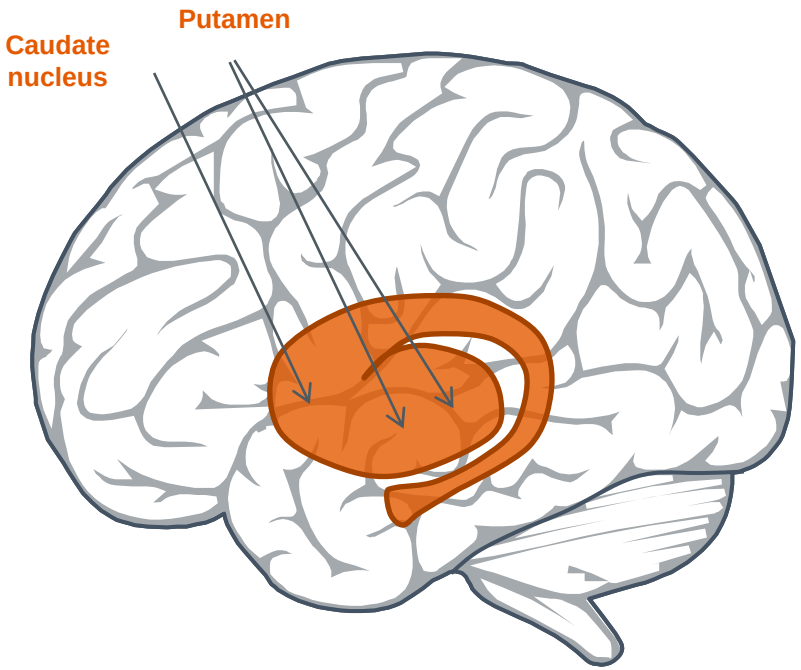
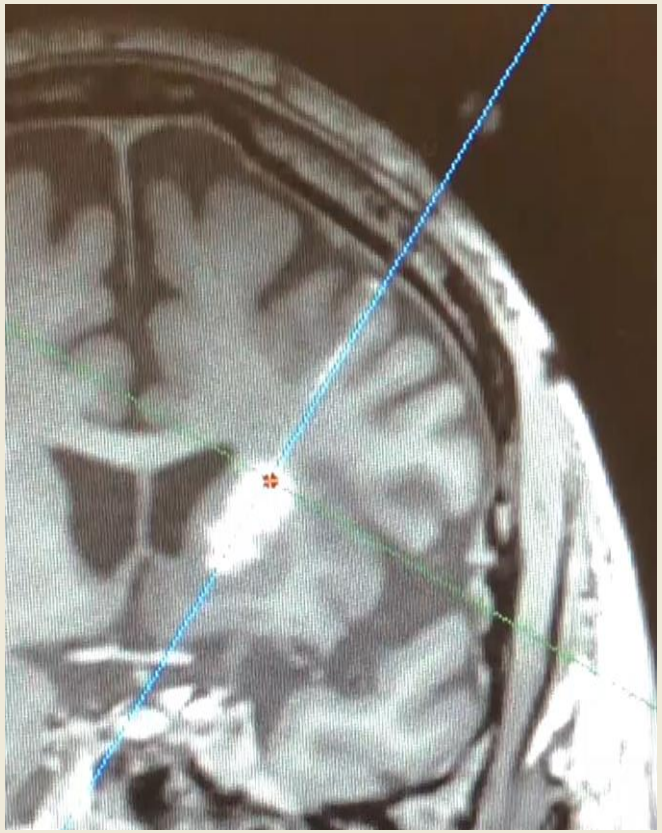


Image reproduced from:
https://www.neuroscientificallychallenged.com/blog/know-your-brain-striatum

Real time MRI visualization using Gd contrast agent

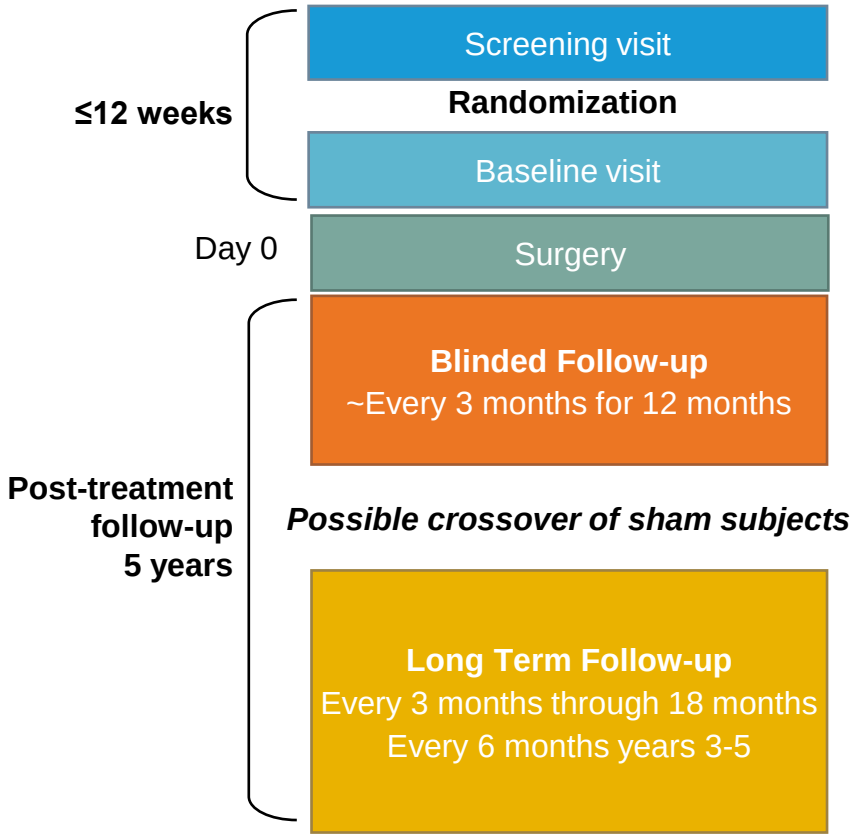


AMT-130: phase I/II U.S. clinical trial design

Inclusion Criteria

- ✓ ≥40 CAG
- ✓ 25 to 65 years of age
- ✓ Total functional capacity (TFC) 9-13
- ✓ Diagnostic Classification Level (DCL) 4 (motor manifest) or 3 (multidimensional)
- ✓ Putamen volume of ≥2.5 cm3 (per side) and caudate volume of ≥2.0 cm3 (per side)
- ✓ Stable concomitant HD medication for 3 months

United States Cohorts 1 and 2



Biomarkers and Endpoints

NfL, mHTT

Volumetric MRI

Total Motor Score
Total Functional Capacity
Stroop Word Test
Symbol Digit Modality Test
cUHDRS

HD GeneTRX1

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

15 Patients

- Low-dose 6e12 AMT-130 (6 patients)
- High-dose 6e13 AMT-130 (9 patients)

12/15 patients in HD-GTRX2 have received AMT-130
Enrollment expected to be completed in 3Q 2023

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

Characteristic (mean, SD, range as applicable)	Control n = 10	AMT-130 Low-dose n = 6	AMT-130 High-dose n = 10
Males/Females (n)	6/4	2/4	4/6
Age at screening	47.0 (8.3), 34 - 58	49.5 (5.3), 44 - 57	47.8 (10.4), 33 - 65
Time since initial diagnosis (yrs)	2.1 (3.4), 0 - 9	1.2 (1.8), 0 - 4.5	3.0 (3.5), 0 - 10
Cytosine-Adenine-Guanine (CAG) repeats	42.8 (1.3), 40 - 45	42.2 (1.5), 41 - 44	41.8 (1.8), 40 - 46
CAG-Age-Product (CAP) score	423.2 (62.7), 317.5 - 541.7	417.7 (58.2), 322.9 - 485.9	380.2 (76.5), 278.9 - 495.0
Total Functional Capacity (TFC)	12.0 (1.1), 10 - 13	12.0 (0.9), 11 - 13	11.9 (1.6), 9 - 13
Total Motor Score (TMS)	12.3 (5.0), 5-19	14.5 (6.7), 8-23	13.9 (5.9), 6-26
Composite UHDRS (cUHDRS)	15.06 (1.47), 11.8 - 16.8	14.7 (2.66), 11.5 - 18.28	14.4 (2.60), 10.89 - 19.63
Disease confidence level DCL 3 /4 (n)	4/6	1/5	2/8
PIN Score	0.95 (0.59)	0.97 (0.78)	0.88 (0.82)

AMT-130: safety and tolerability

- AMT-130 was generally well-tolerated across both dose cohorts
- No treatment emergent adverse events (TEAEs) led to discontinuation of patient follow-up
- Most common treatment emergent adverse events were:
  - Procedural Headache (Control 50%, Low Dose : 57.1% High Dose 63.6%)
  - Procedural Complications (Control 40%, Low Dose : 57.1% High Dose 45.5%)
  - Post-lumbar puncture syndrome (Control 60%, Low Dose : 28.6% High Dose 36.4%)
  - Procedural Pain (Control 50%, Low Dose : 28.6% High Dose 36.4%)
  - Headache (Control 30%, Low Dose : 28.6% High Dose 40.5%)
- There were no clinically relevant differences between treatment groups in vital signs, laboratory values or ECG

AMT-130: safety and tolerability

- Severe Adverse Events (SAEs) occurred more often in the AMT-130 treatment groups
  - Low dose (n=2): post-operative delirium, major depression, suicidal ideation
  - High dose (n=2): back pain, tension headache, CNS inflammation, post-lumbar puncture syndrome
  - Control (n=1): deep vein thrombosis
- Two SAEs (severe headache, CNS inflammation) in the higher dose group were reported as a suspected unexpected serious adverse event attributed to AMT-130. Both have resolved.

Following a review of the interim data analysis, the DSMB concluded that there are no safety concerns with either dose and recommended continuing clinical development of AMT-130

AMT-130: natural history comparators with and without a minimum striatal volume

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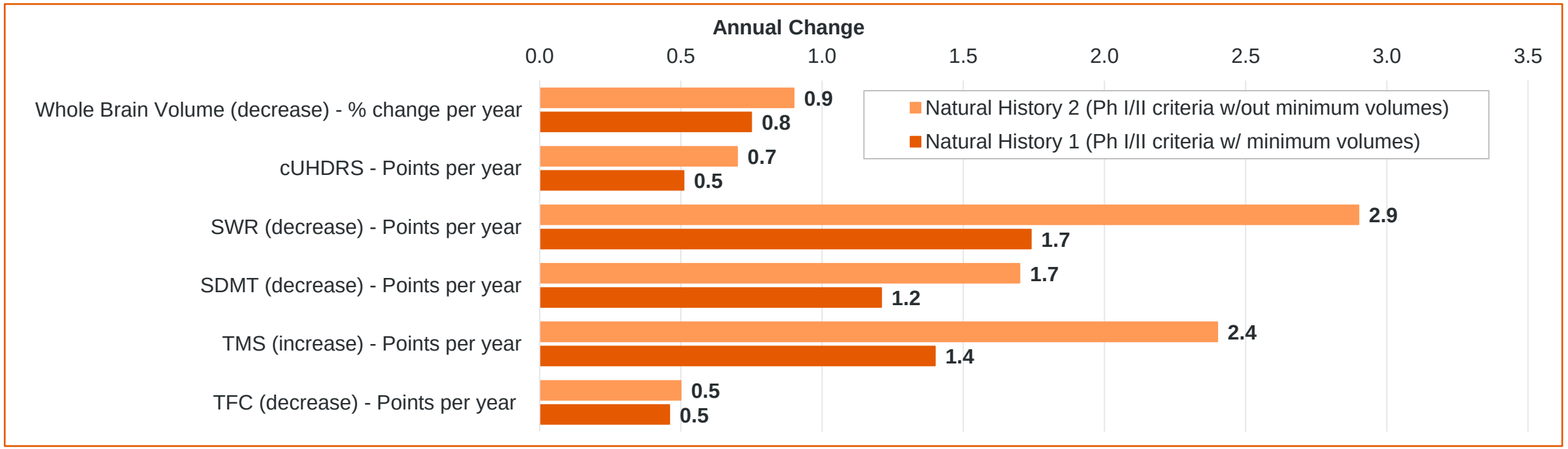
Natural History Cohort 2 includes TRACK-HD patients that closely match the study's clinical inclusion criteria.

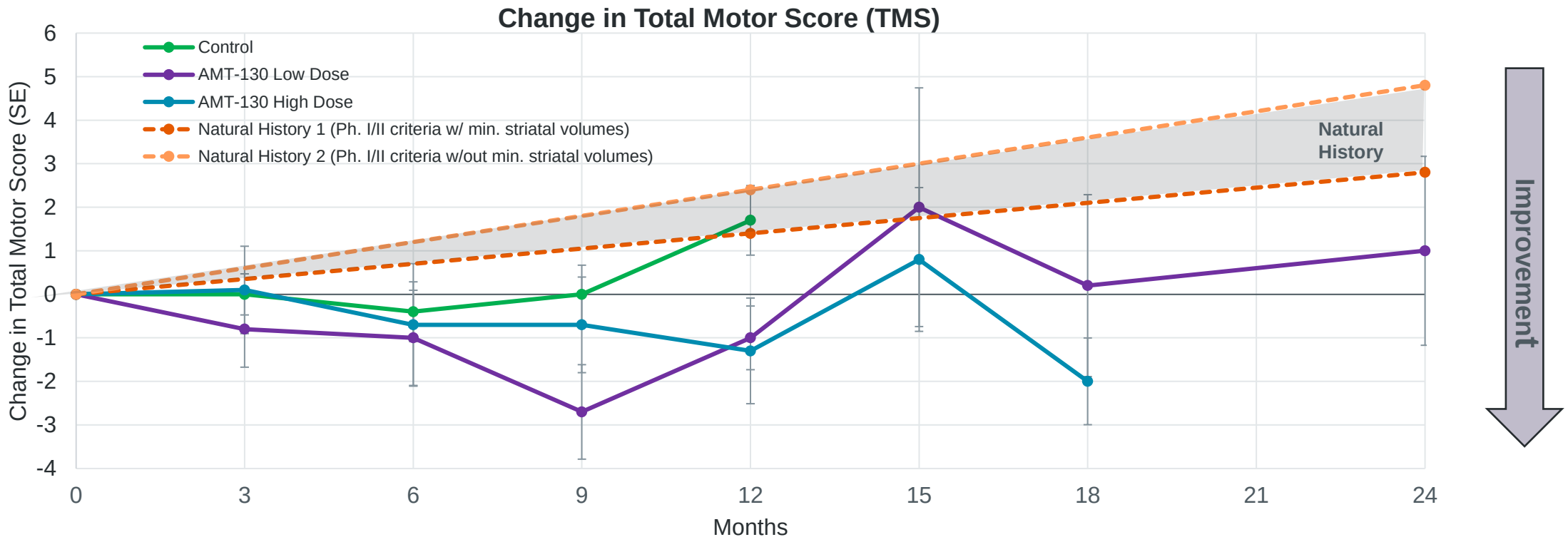
Natural History Cohort 1 is the subgroup of patients from cohort 2 that exceed the minimum striatal volumes.



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

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

AMT-130: treated patients improved in TMS relative to controls and natural history



Patients	Base	3M	6M	9M	12M	15M	18M		24M
Low Dose	6	6	6	6	6	6	6		5
High Dose	10	10	10	10	9	4	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.

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

AMT-130: treated patients preserved TFC scores relative to baseline and improved compared to controls and natural history

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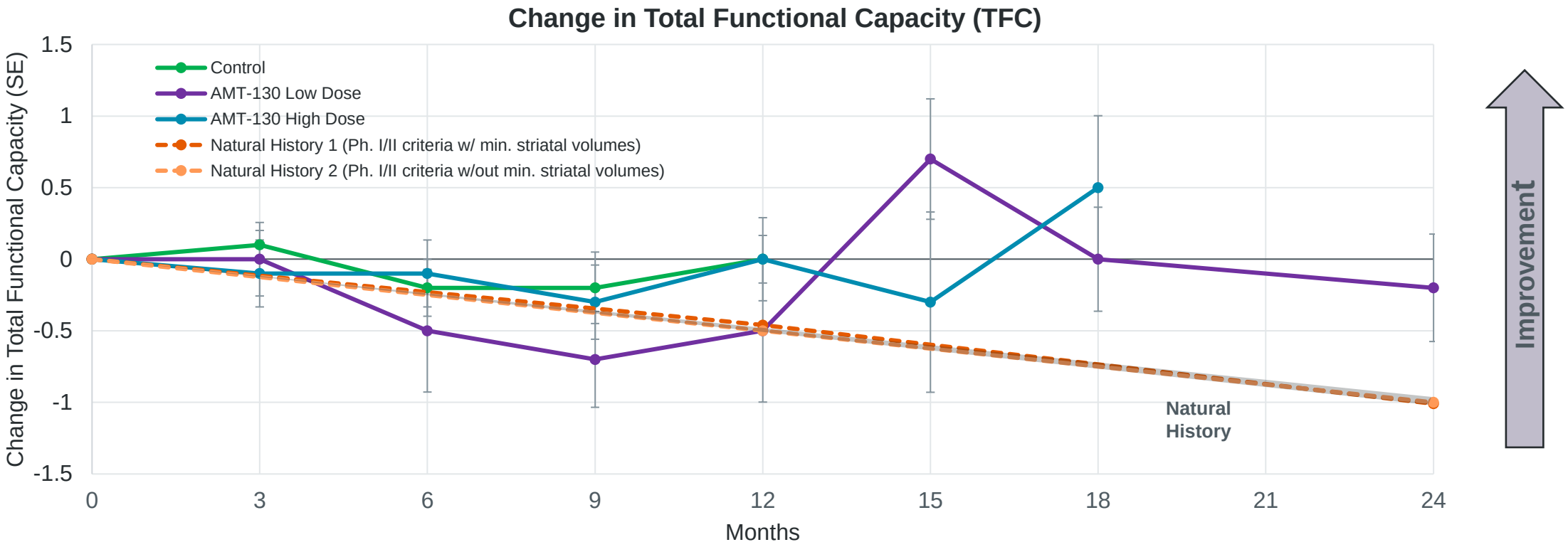

Patients	Base	3M	6M	9M	12M	15M	18M		24M
Low Dose	6	6	6	6	6	6	6		5
High Dose	10	10	10	10	9	4	2		
Control	10	10	10	10	9				

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 GeneTRX1

AMT-130: treated patients preserved function in SWT relative to baseline and improved compared to natural history

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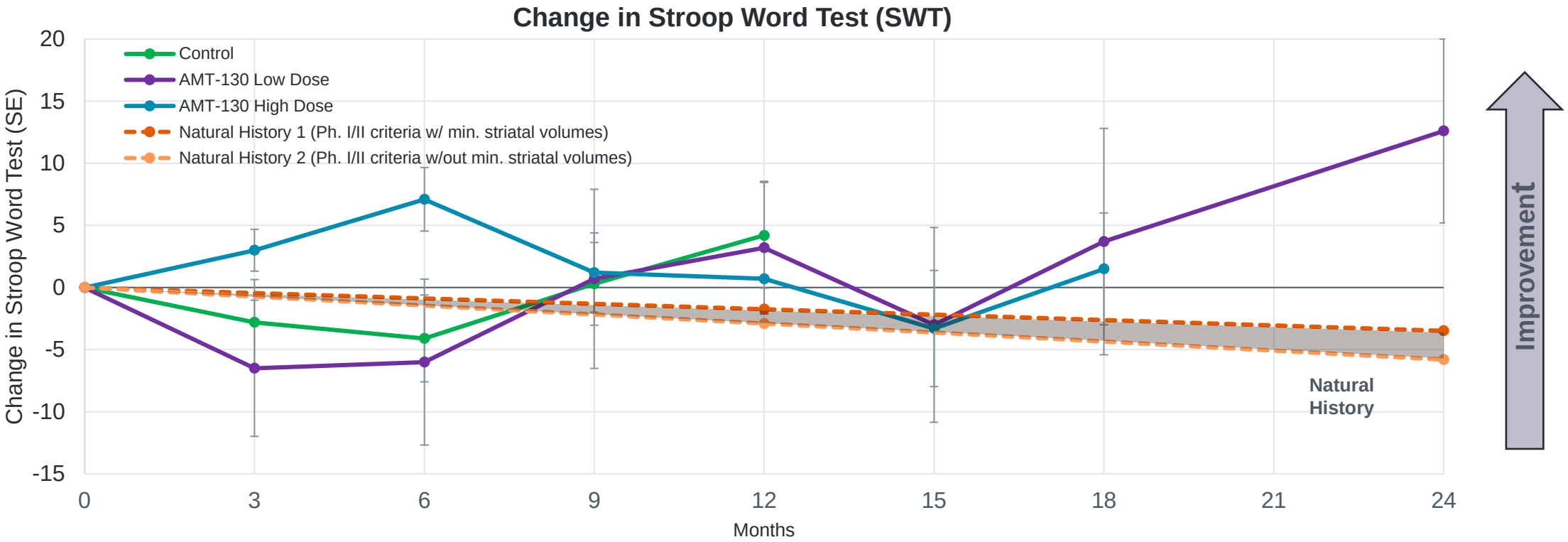

Patients	Base	3M	6M	9M	12M	15M	18M		24M
Low Dose	6	6	6	6	6	6	6		5
High Dose	10	10	10	10	9	4	2		
Control	10	9	10	10	9				

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).

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

HD GeneTRX1

AMT-130: high-dose treated patients are favorable to natural history and controls in SDMT

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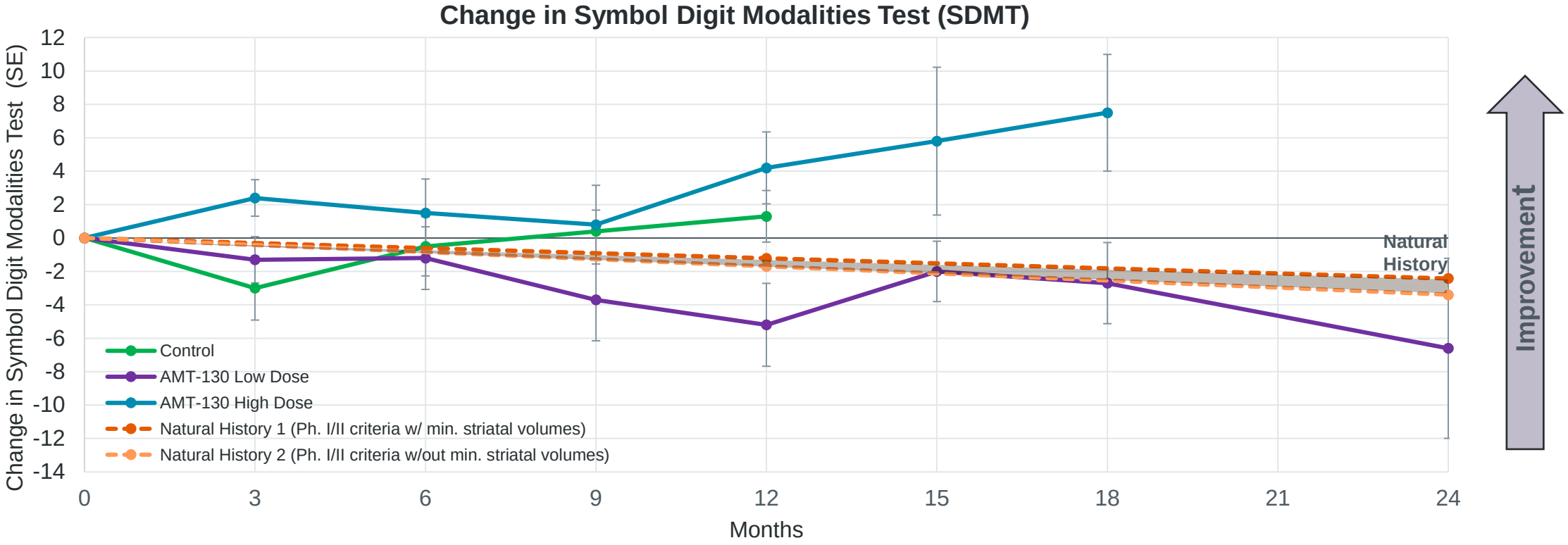

Patients	Base	3M	6M	9M	12M	15M	18M		24M
Low Dose	6	6	6	6	6	6	6		5
High Dose	10	10	10	10	9	4	2		
Control	10	9	10	10	9				

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)

AMT-130: treated patients preserved cUHDRS relative to baseline and improved compared to natural history

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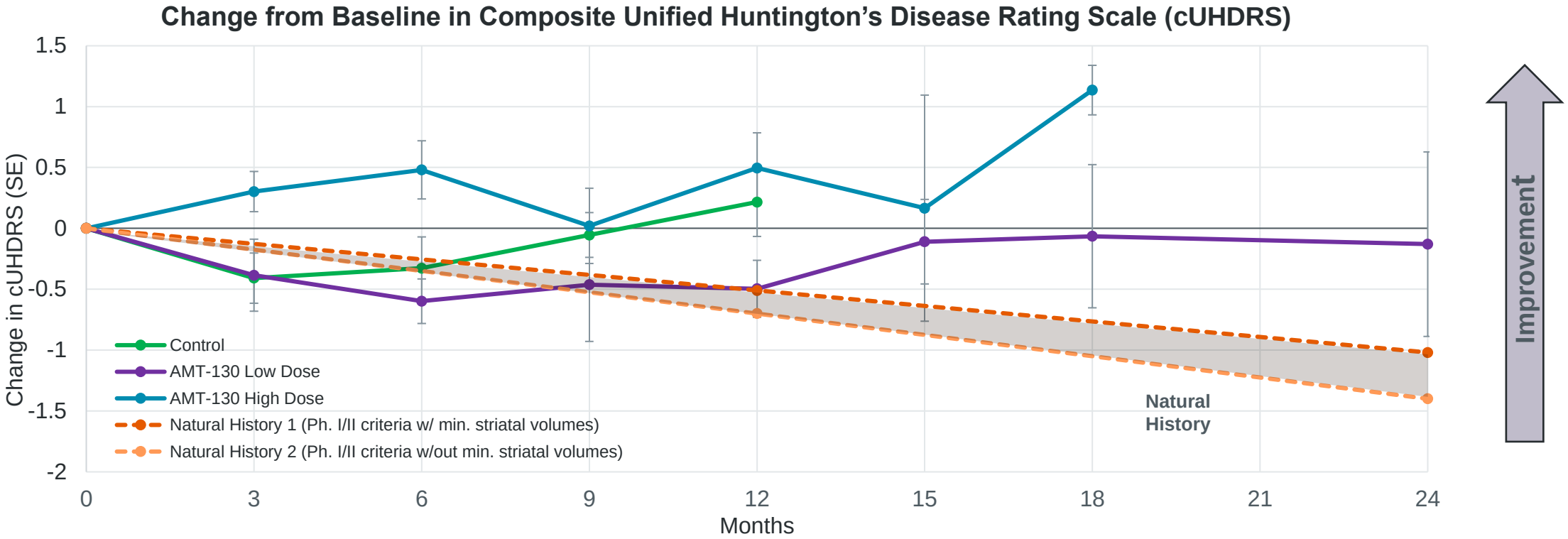

Patients	Base	3M	6M	9M	12M	15M	18M		24M
Low Dose	6	6	6	6	6	6	6		5
High Dose	10	10	10	10	9	4	2		
Control	10	8	10	10	9				

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 (SWR)

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

HD GeneTRX1

uniQure AMT-130: clinical and functional data conclusions

- Based on a small number of treated patients with limited follow up, there is an early indication of a potentially positive clinical effect of AMT-130 on disease progression
- Patients treated with the low-dose of AMT-130 have generally preserved function at 24 months relative to the baseline and relative to the natural history across most clinical measures
- Patients treated with the high-dose are trending favorably to the natural history across all functional measures and slightly better than patients receiving the low-dose through 12-18 months
- Patients in the control group experienced a worsening of the Total Motor Score at 12 months in line with the natural history, but had preserved function in other clinical measures

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Biomarker: Neurofilament Light Chain (NfL)

Phase I/II U.S. Clinical Trial

AMT-130: NfL is below baseline and natural history in low-dose cohort and declining towards baseline in high-dose cohort

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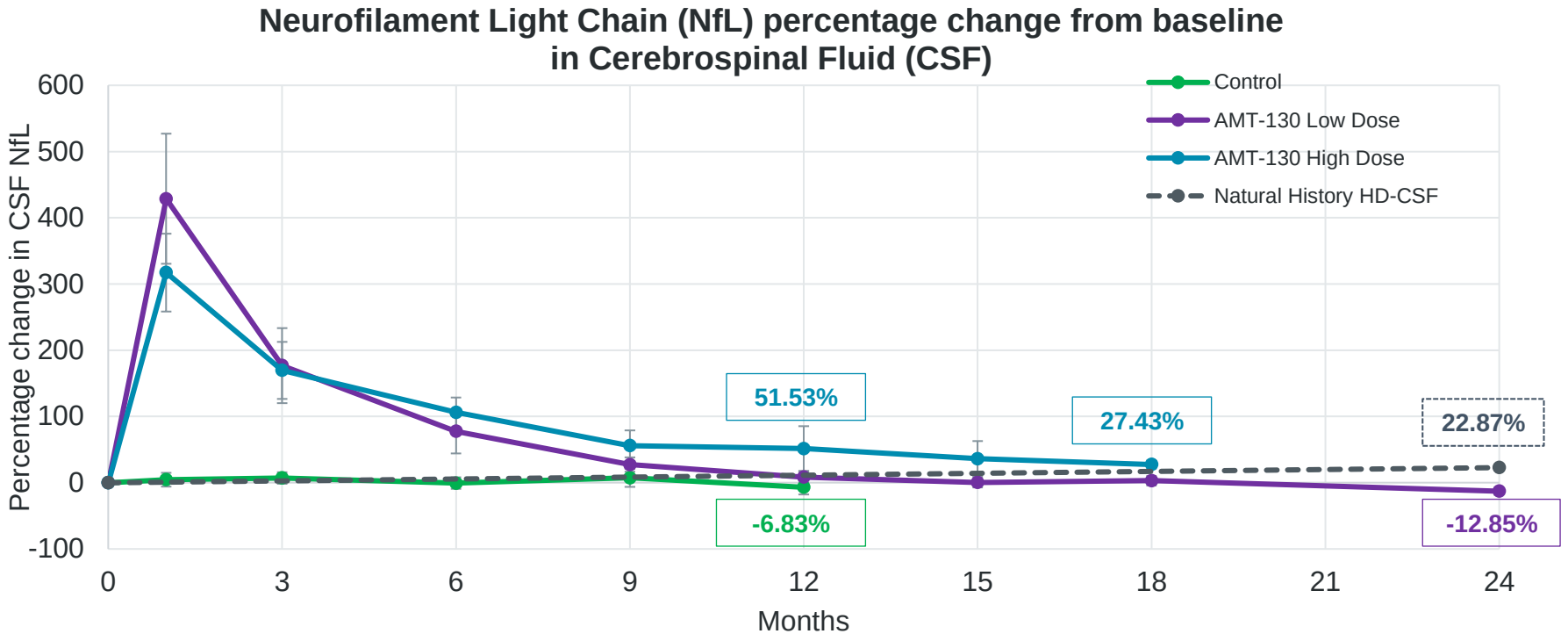

Patients	Base	1M	3M	6M	9M	12M	15M	18M		24M
Low-Dose	6	6	5	6	6	6	6	6		5
High-Dose	10	10	9	10	10	8	4	2		
Control	10	9	9	9	7	7				

- As expected, CSF NfL increases immediately after surgery and declines after approximately one month; Increases are not dose dependent
- In the low-dose group, average CSF NfL is below baseline and natural history at 24 months
- In the high-dose group, average CSF NfL is declining towards baseline at 12 months

Natural History HD-CSF (Rodrigues 2020) - n=19 met our inclusion criteria and had baseline value and at 24 months

HD GeneTRX1

AMT-130: NfL trends in treated patients continue to be encouraging at 12- and 24-months

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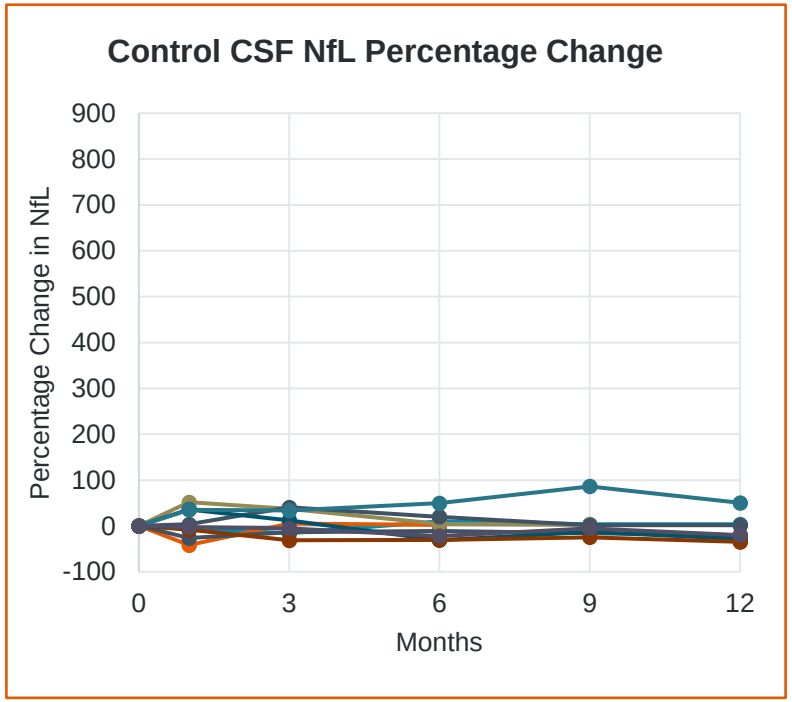
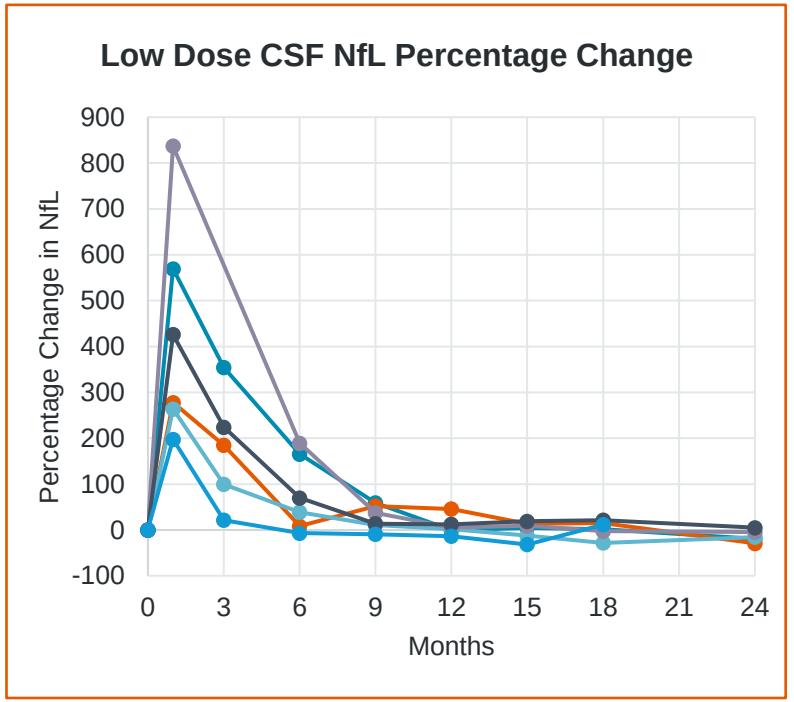
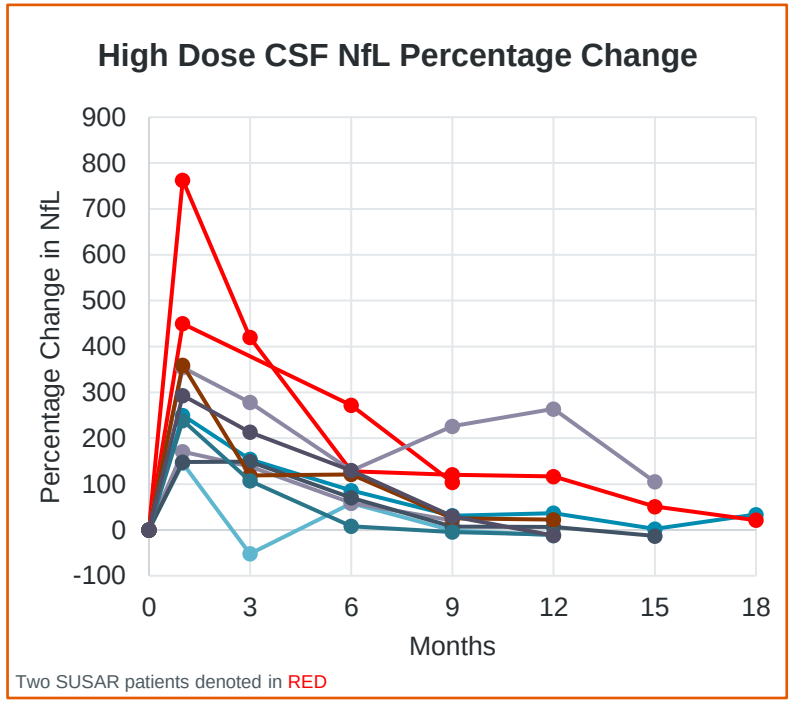
NfL levels are below baseline in 4 of 5 evaluable low-dose patients at 24 months and 4 of 8 high-dose patients with at least 12 months of follow-up







uniQure AMT-130: NfL conclusions

- As expected, an increase in CSF NfL occurred immediately after the surgical procedure
- The initial NfL spikes are not dose-dependent and are likely related to the surgical intervention
- CSF NfL continued to decline in the low-dose cohort and was below baseline and natural history at 24 months
- CSF NfL is declining towards baseline at 12 months in patients receiving the high dose

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Biomarker: Mutant HTT

Phase I/II U.S. Clinical Trial

AMT-130: mHTT reduced in treated patients in low-dose cohort relative to baseline and control

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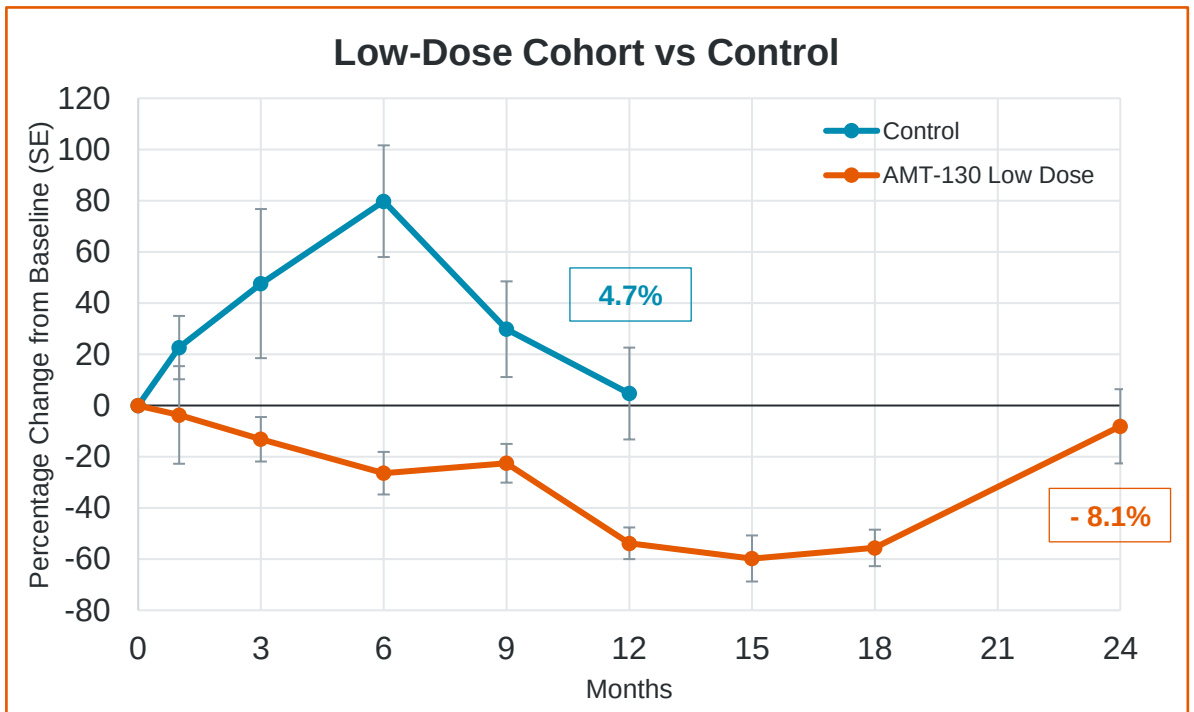
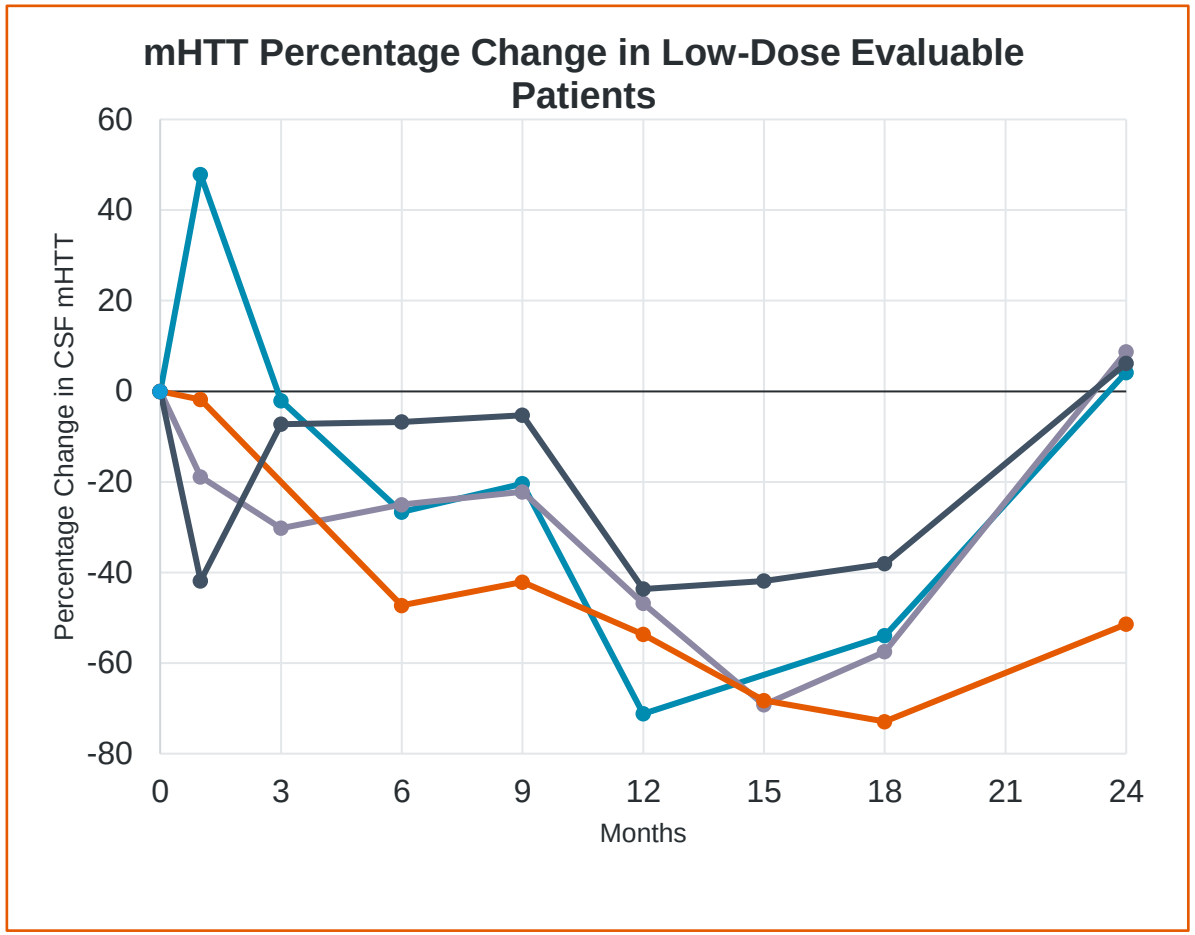


Patients	Base	1M	3M	6M	9M	12M	15M	18M		24M
Low Dose	4	4	3	4	4	4	3	4		4
Control	7	6	7	7	5	6				



Standard Error (SE)

AMT-130: mHTT in CSF is more variable in high-dose cohort, some patients showing evidence of reductions

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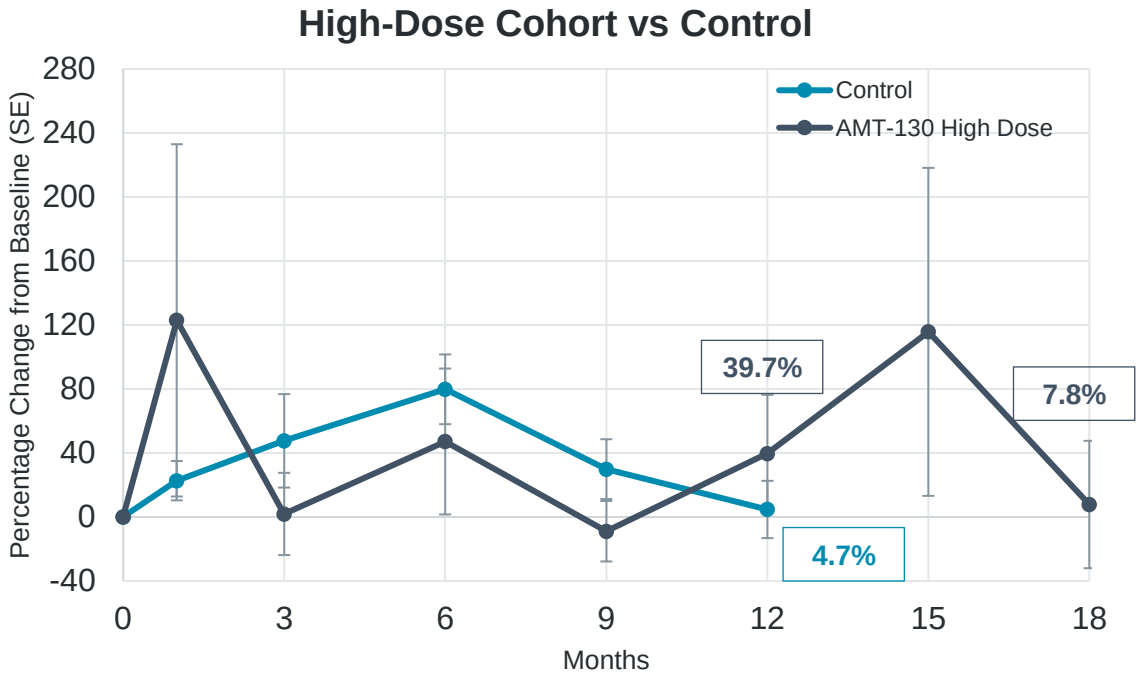
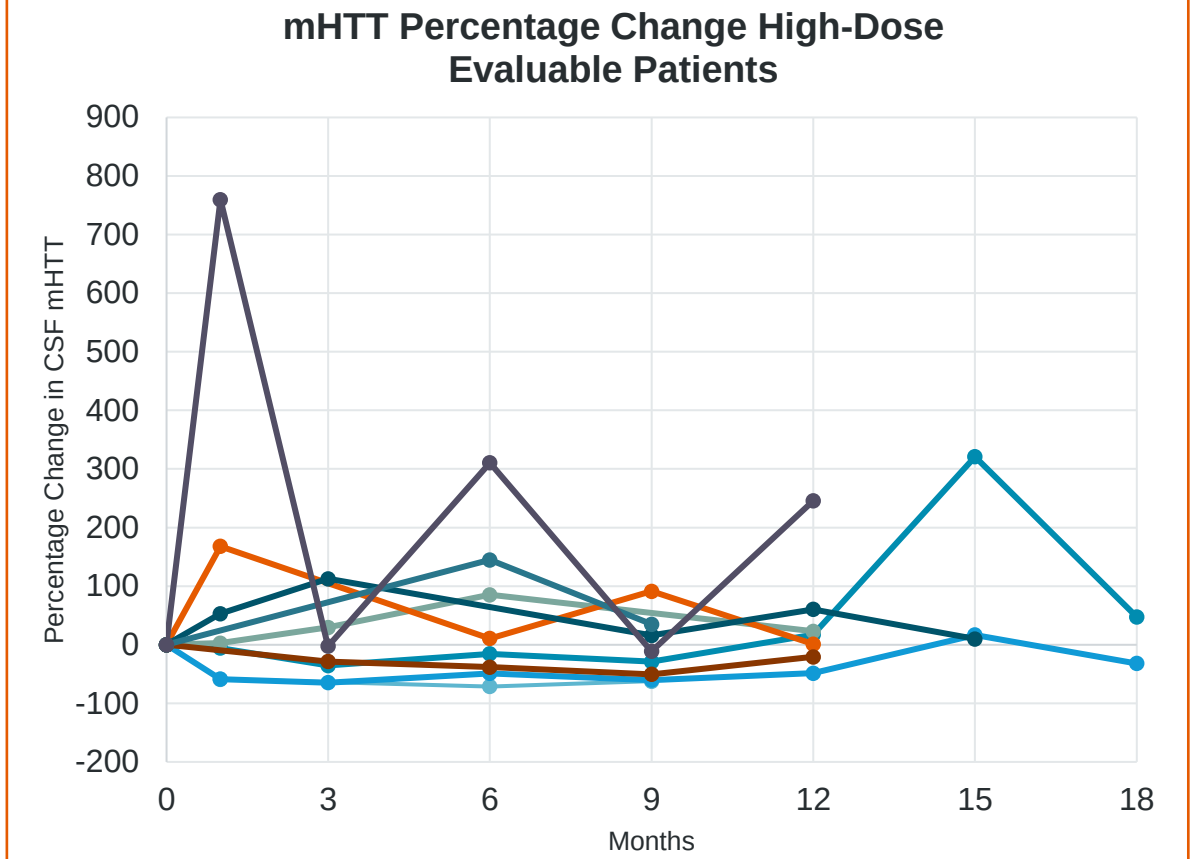


Patients	Base	1M	3M	6M	9M	12M	15M	18M
High Dose	9	7	6	8	8	7	3	2
Control	7	6	7	7	5	6		



Standard Error (SE)

AMT-130: mHTT in CSF is generally above baseline in the control patients

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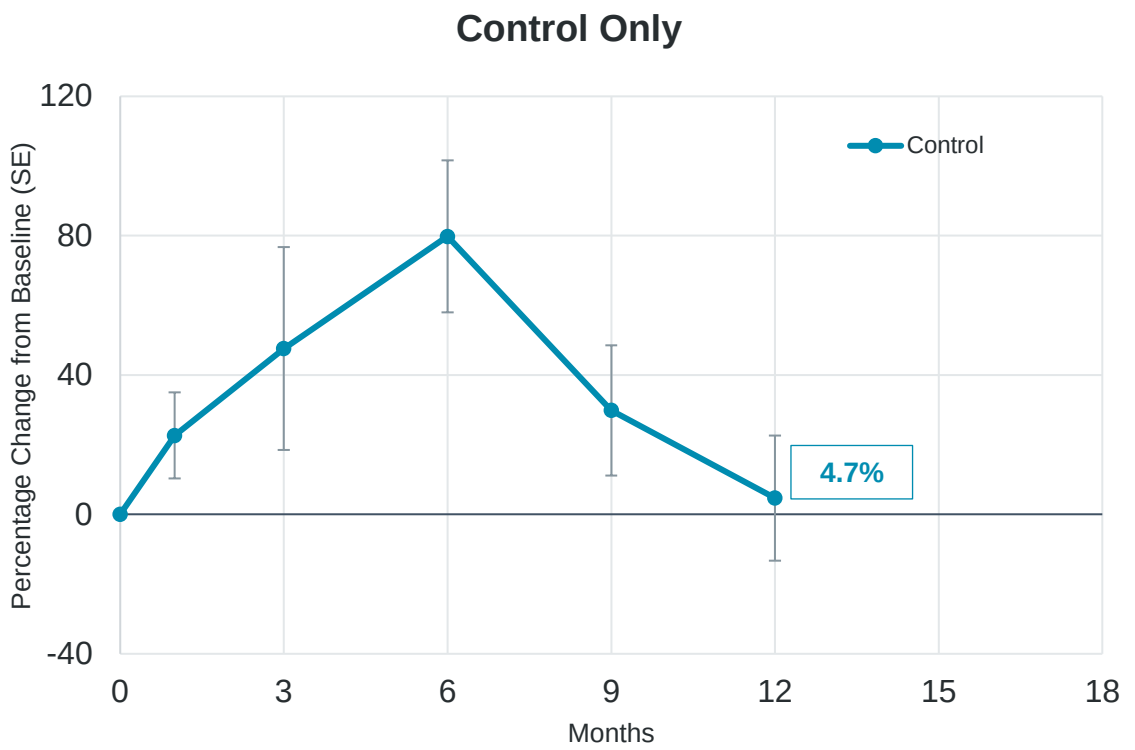
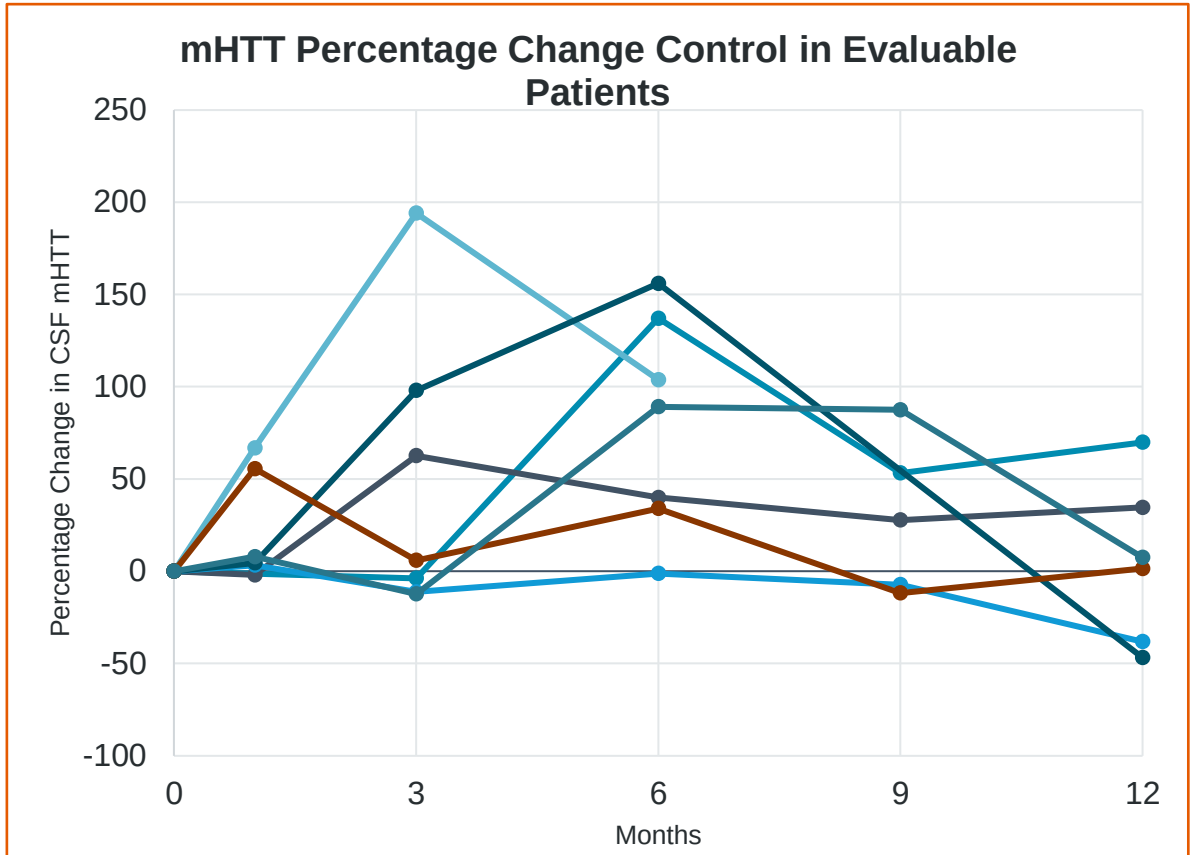


Patients	Base	1M	3M	6M	9M	12M	15M	18M
Control	7	6	7	7	5	6		



Standard Error (SE)

AMT-130: mHTT conclusions

- Interpatient variability in mHTT data is potentially related to inherent limitations of the assay
- Reduction of mHTT in the low-dose cohort supports AMT-130 target engagement
- High variability in mHTT was observed in the high-dose cohort, with 3 of 9 patients below baseline at the last available measurement
- In control group, 5 of 7 evaluable patients had mHTT above the baseline at the last available measurement

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Imaging Data

Phase I/II U.S. Clinical Trial

AMT-130: whole brain volume is not significantly impacted by treatment

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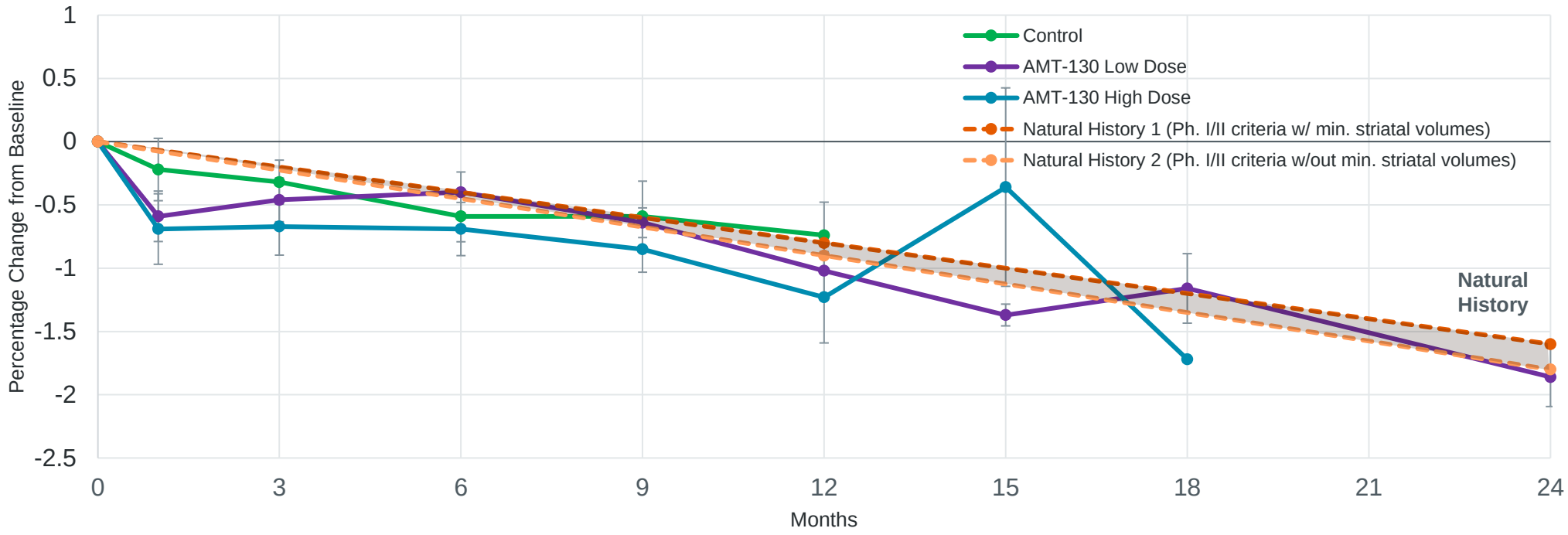
Whole Brain Volume Percentage Change



Patients	Base	3M	6M	9M	12M	15M	18M		24M
Low Dose	6	6	5	6	6	6	6		5
High Dose	10	10	10	10	8	3	2		
Control	10	10	10	10	9				

AMT-130: volumetric MRI imaging

- Whole brain volume: There is no statistically significant difference between the loss of whole brain volume in patients treated with AMT-130 versus controls
- Ventricular volume: Patients treated with both doses of AMT-130 have a greater increase in ventricular volume than patients in the control arm. The increase in ventricular volume does not appear to be dose dependent.
- Striatal Volume (caudate and putamen): Volumetric imaging of the striatum was confounded by changes of structural boundaries associated with direct drug infusion into these structures.
- Volume changes were not associated with clinical signs or symptoms in the majority of patients.

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Interim Analysis Conclusions

Phase I/II U.S. Clinical Trial

AMT-130: summary and conclusions

Promising data show early trends of a positive impact on disease progression and support continued development of AMT-130

- AMT-130 was generally well-tolerated with a manageable safety profile
- Patients treated with both doses of AMT-130 show early evidence of preserved function relative to baseline and clinical benefit relative to natural history
- CSF NfL was below baseline and natural history at 24 months in low-dose patients and is declining towards baseline in high-dose patients at 12 months
- Transient increases in CSF NfL are not dose-dependent and are likely related to the surgical procedure, with subsequent declines in all patients
- mHTT levels in CSF were highly variable but showed declines in low-dose patients and several high-dose patients

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AMT-130 Clinical Program Next Steps

AMT-130: next steps in clinical development

- Q3 2023: Completion of enrollment in Phase I/II trial in EU/UK
- 2H 2023: Initiation of Cohort 3 in Phase I/II trial in the U.S. to investigate the effects of immunosuppression on perioperative safety
- Q4 2023: Clinical update on Phase I/II trial including additional 18- and 30-month data on US cohorts and 12-month follow-up on low-dose cohort from EU/UK study
- Q1 2024: Meeting with regulators to discuss data and potential path forward for clinical development

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Closing Remarks

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