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Phase I/II AMT-130 Huntington's Disease Program Update

July 9, 2024

uniQure Disclaimer

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. Examples of these forward-looking statements include, but are not limited to, statements concerning: our plans to meet with regulatory authorities to discuss the potential for expedited clinical development; the timing of our planned meeting and discussions with regulatory authorities; our ability to continue accumulating long-term patient data; the potential clinical and functional effects of AMT-130; our plans to continue clinical development of AMT-130; the potential for accelerated regulatory pathways; our use of a natural history cohort as a basis for comparison with respect to the efficacy of AMT-130; our enrollment plans with respect to the third cohort studying AMT-130 in combination with immunosuppression and our plans to present safety data from this cohort; the utility of NfL in CSF as an effective biomarker and indicator of clinical severity; and our plans to present further interim analyses. Because these statements are subject to risks and uncertainties, our actual results could differ materially from those expressed in these forward-looking statements. These risks and uncertainties include, among others: risks related to our clinical trials of AMT-130, including the risk that such trials will be unable to demonstrate data sufficient to support further clinical development and the risk that interim data from the trials may not be predictive of later data readouts; risks related to our ability to pursue business development efforts with respect to AMT-130; risks related to our planned interactions with regulatory authorities, which may affect the initiation, timing and progress of clinical trials and pathways to regulatory approval; risks related to our use of propensity-weighted external controls in connection with its statistical analysis of clinical outcomes to date, and whether regulatory authorities will accept our approach as a basis for accelerated approval; risks related to our use of nominal p values as a basis for its statistical analyses; whether the measurements that we are evaluating continue to be viewed as robust and sensitive measurements of disease progression; whether RMAT designation or any accelerated pathway, if granted, will lead to regulatory approval; our ability to conduct and fund a Phase III or confirmatory study for AMT-130; our ability to continue to build and maintain the infrastructure and personnel needed to achieve our goals; our effectiveness in managing current and future clinical trials and regulatory processes; our ability to demonstrate the therapeutic benefits of our gene therapy candidates in clinical trials; the continued development and acceptance of gene therapies; our ability to obtain, maintain and protect our intellectual property; and our ability to fund our operations and to raise additional capital as needed and on acceptable terms. These and other risks and uncertainties are described more fully under the heading “Risk Factors” in our periodic filings with the U.S. Securities and Exchange Commission (“SEC”), including in our Annual Report on Form 10-K filed with the SEC on February 28, 2024, and other filings that we make with the SEC from time to time.

Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements and, except as required by law, we assume no obligation to update these forward-looking statements to reflect events that occur or circumstances that exist after the date on which they were made.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third -party sources. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

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Opening Remarks

Matt Kapusta
Chief Executive Officer

Slowing progression of Huntington's disease could extend patients' quality of life

HD is a progressive neurodegenerative disease with **no disease-modifying treatments available.**

AMT-130 aims…

1. To **slow the rate of disease progression**
2. To provide HD patients with an **improved quality of life**

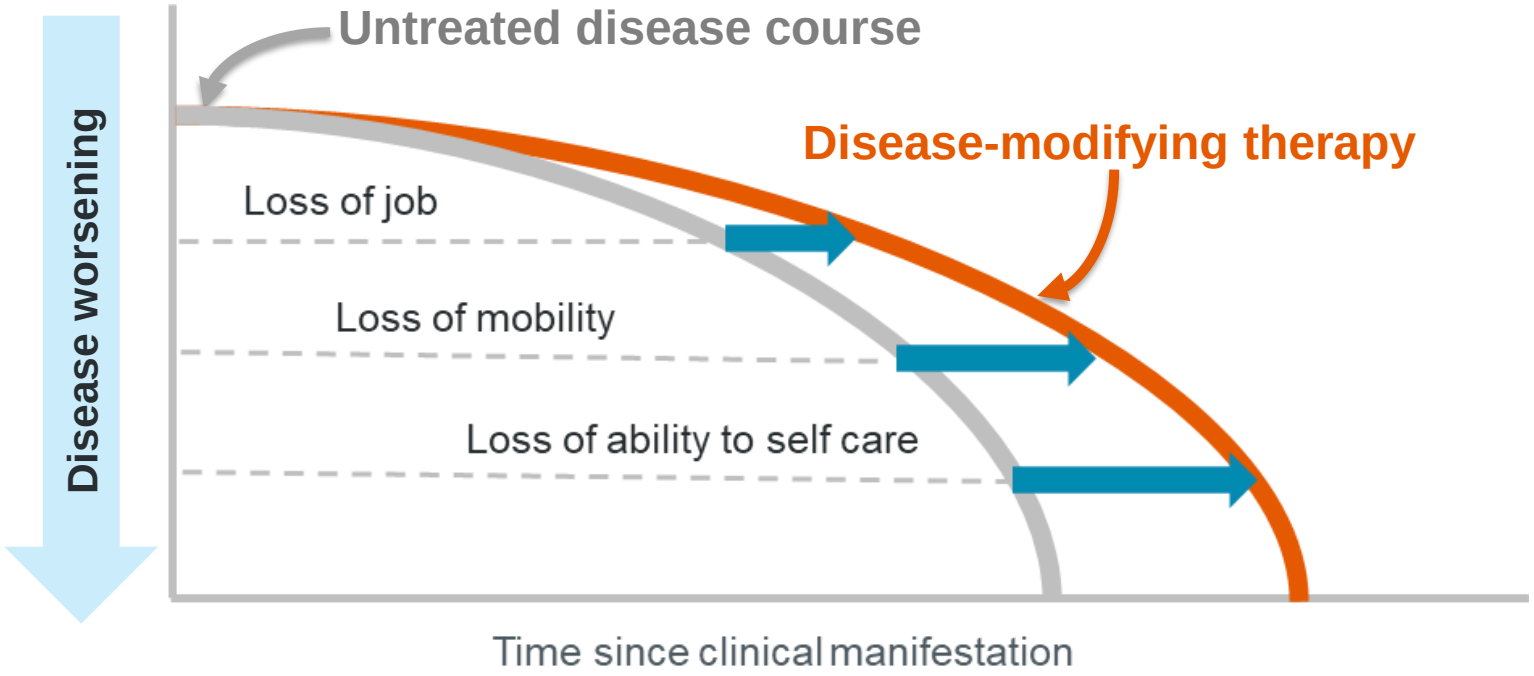


Illustration depicts potential benefits of disease modifying treatment.

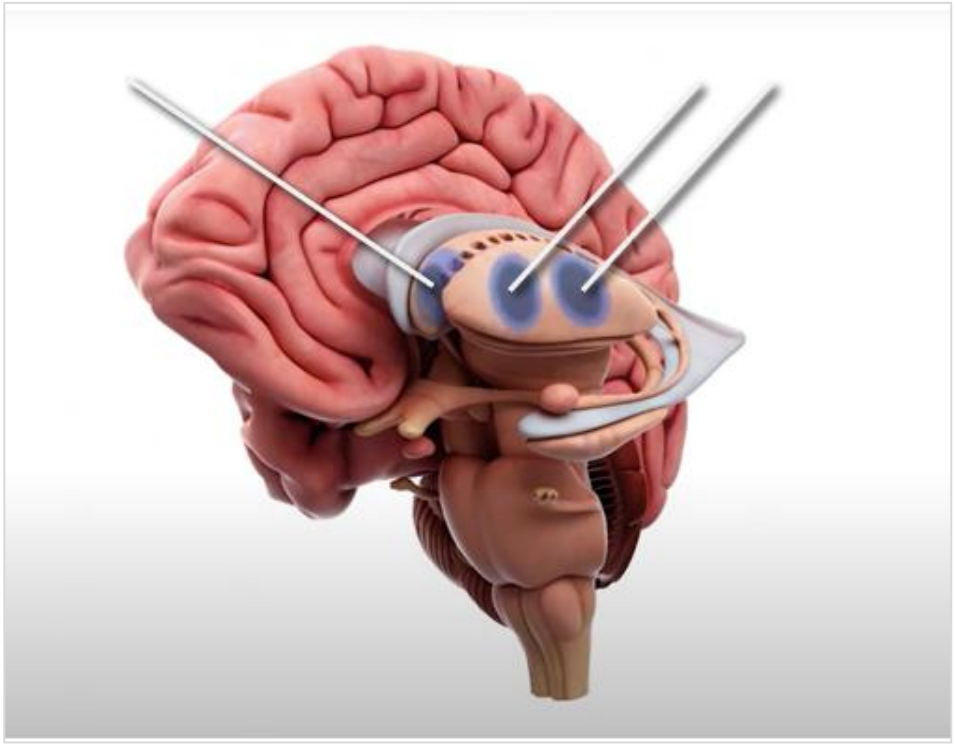
Abbreviations: HD, Huntington's Disease.
References: Ross CA, *et al. Nat Rev Neurol*. 2014; 10(4): 204-16.

A promising approach to treat Huntington's disease

AMT-130 is a gene therapy candidate in Phase I/II clinical trials in the US and Europe to investigate the slowing of disease progression in HD patients with early-to-moderate disease.

Key AMT-130 differentiators:

- **One-time administration** with potentially long-term effects
  - Potential for early therapeutic intervention
  - Ability to accumulate long-term clinical data to support efficacy
- **Direct delivery and spread** across diseased areas of brain
  - MoA demonstrated across multiple animal species
  - Leverages proprietary miQURE gene silencing platform
- **Suppression of highly toxic exon-1 splice isoform** in addition to full-length mHTT



Abbreviations: HD, Huntington's Disease; miRNA, microRNA.
References: https://www.neuroscientificallychallenged.com/blog/know-your-brain-striatum. Accessed June 2024. Data on file. June 2024.

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Key Updates

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

uniQure AMT-130 key updates

At 24 months, AMT-130 demonstrated a statistically significant slowing of progression compared to a robust external control, and reductions in a key marker of neurodegeneration.

Clinical Measures

Statistically significant and **dose-dependent slowing of disease progression** as measured by **cUHDRS**

Neurodegeneration

Statistically significant reduction in **CSF NfL** compared to baseline

Safety Profile

Generally well-tolerated with a **manageable safety profile at both doses; No new SAEs** related to AMT-130

Regulatory

Received **RMAT** designation; Discussions for potential **accelerated approval pathway** with **FDA 2H 2024**

Abbreviations: CSF, cerebrospinal fluid; NfL, neurofilament light chain; SAEs, serious adverse events; FDA, Food & Drug Administration; RMAT, Regenerative Medicine Advanced Therapy. **References:** Data on file, June 2024. All p-values are nominal and unadjusted. Statistical comparisons of patients treated with AMT-130 to the propensity score-weighted external control were conducted on a post-hoc basis

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External Comparator & Clinical Measures

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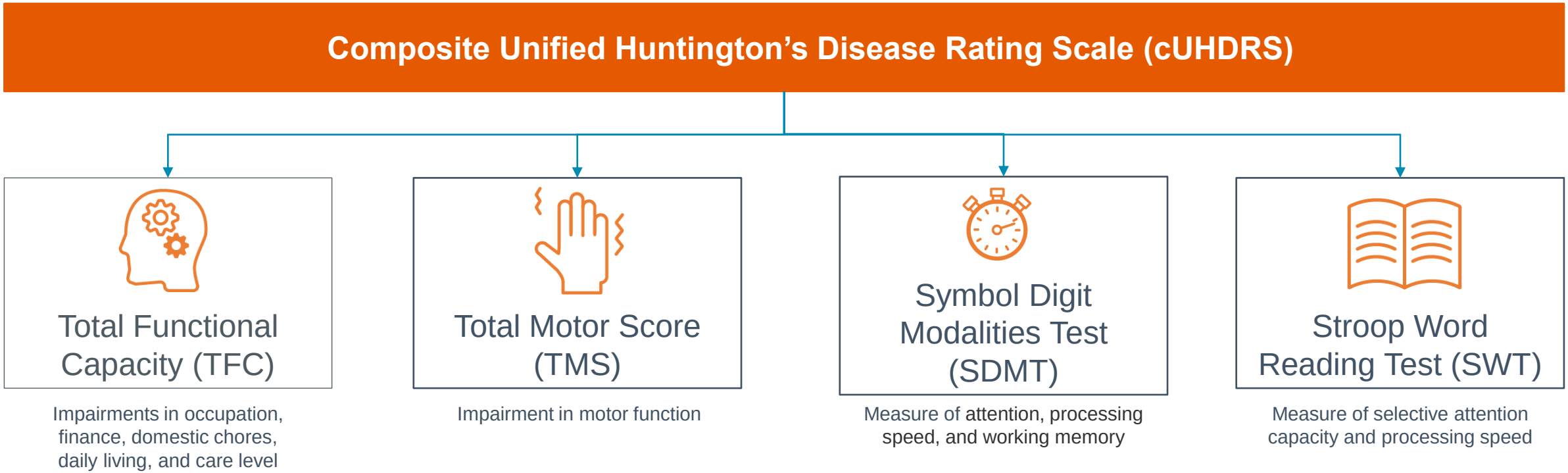
The Composite Unified Huntington's Disease Rating Scale is a widely used efficacy outcome measure



References Neurology 2017;89:2495–2502

cUHDRS has been shown to be the most sensitive measure of progression of Huntington's disease

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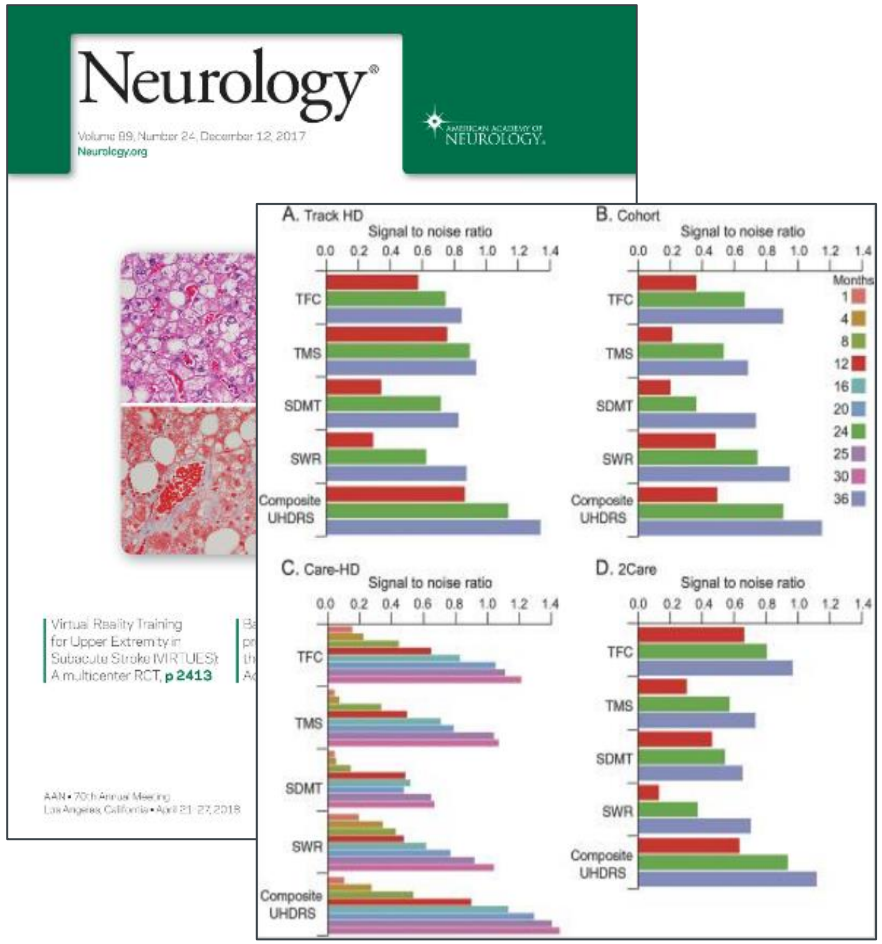
An independent study demonstrated that **cUHDRS best characterizes the clinical progression of HD** and provides an **opportunity for enhanced clinical trial efficiency relative to individual measures.**

The study was based on 1,668 patients with early HD prospectively followed for up to 30-36 months.



Abbreviations: cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's Disease.
References: Schobel et al. Neurology 2017;89:2495–2502.

AMT-130 is the first Huntington disease drug candidate to receive RMAT designation

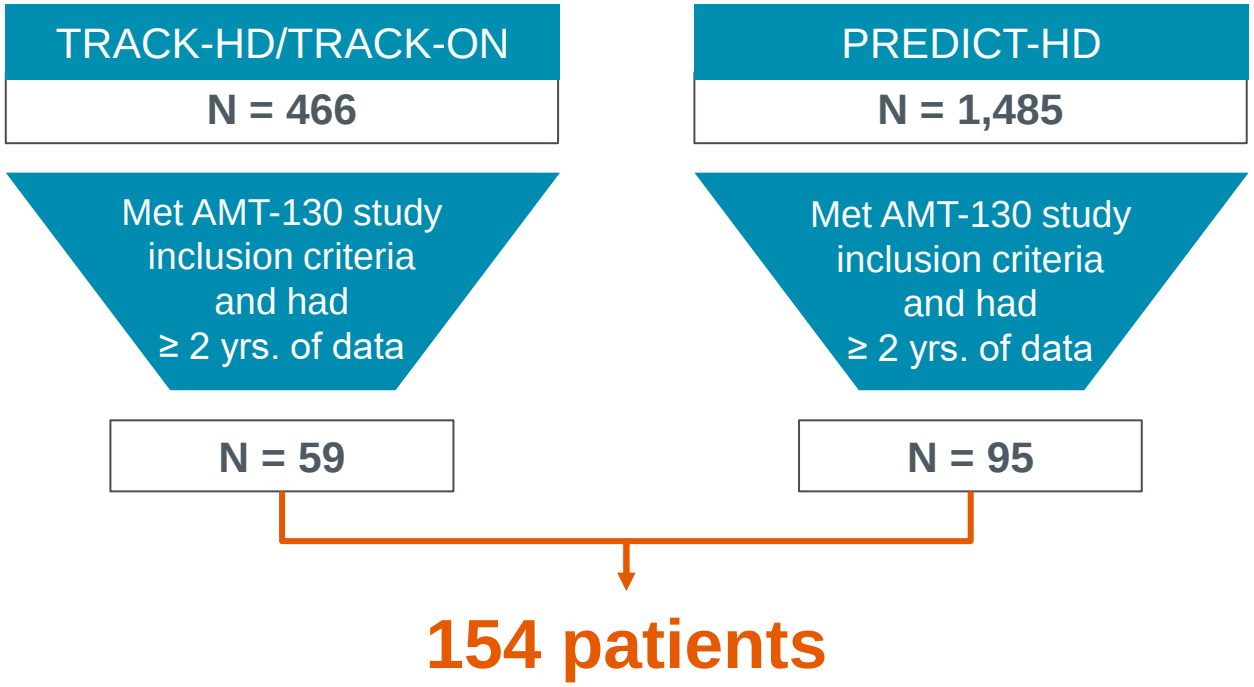
RMAT designation allows for more frequent interactions with regulators, accelerated approval based on surrogate endpoints and potential eligibility for priority review.

- RMAT designation granted in June 2024
- Based on data from the December 2023 update
- Data submitted to the FDA included 8 treated subjects with 24 months of follow-up and another 17 subjects with 12-24 months of follow-up
- Statistical analyses using a propensity-based methodology showed evidence of potential benefit compared to a matched natural history cohort
- Today's update builds on what was presented to the FDA, and includes 21 treated subjects with 24 months of follow-up

New expanded natural history cohort supported RMAT application

Natural History Cohort was expanded to better evaluate efficacy.

- Longitudinal, prospectively collected data
- Consistent and regular rater training similar to clinical trial settings
- High quality volumetric MRI data in addition to clinical endpoints
- Access to data thanks to a collaboration with CHDI



Abbreviations: HD, Huntington's Disease; CHDI, Cure Huntington's Disease Initiative; MRI, magnetic resonance imaging.
References: Data on file, June 2024.

A Propensity Score-Weighted External Control serves as a robust comparator for two-year efficacy outcomes

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Propensity Score-Weighted External Control (PSW External Control)

- Well-matched natural history controls can play a critical role in assessing treatment effect in clinical trials
- Propensity-score weighting ensures maximum comparability between the external control and treated patients
  - Reduces selection bias
  - Acceptable in regulatory submissions
- We conducted a propensity-score weighted analysis using the 154-patient natural history cohort
- Propensity scores were calculated based on eight prognostic factors[1]
- Baseline characteristics of the PSW External Control are nearly identical to those of patients treated with AMT-130
- The PSW External Control is a more robust comparator to evaluate the potential treatment effect of AMT-130 at 24 months

(1) Prognostic factors include CAG (cytosine-adenine-guanine) repeats; CAP (CAG-Age-Product) Score; cUHDRS (composite Unified Huntington's Disease Rating Scale); DCL (diagnostic confidence level); PIN Score (Prognostic Index), and TFC (Total Function Capacity).

Baseline demographics and disease characteristics well-matched across groups

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The propensity score-weighted external control has **well-matched baseline characteristics** to the patients treated with AMT-130.

Demographics and Characteristics Mean (SD)	**AMT-130 patients w/ 24 months follow-up (n = 21)**	**PSW External Control (n = 154)**
Males (%)	57.1%	56.8%
Age	46	45
CAG repeats	43	43
CAP score	88	86
DCL = 4	76.2%	76.6%
PIN Score	0.95	0.84
cUHDRS	14.2	14.4
TFC	11.9	11.8

Abbreviations: CAG, cytosine-adenine-guanine; CAP, CAG-Age-Product; cUHDRS, composite Unified Huntington's Disease Rating Scale; DCL, diagnostic confidence level; PIN, Prognostic Index; TFC, Total Function Capacity.
References: Data on file, June 2024.

AMT-130 demonstrated dose-dependent slowing of disease progression in cUHDRS at 24 months

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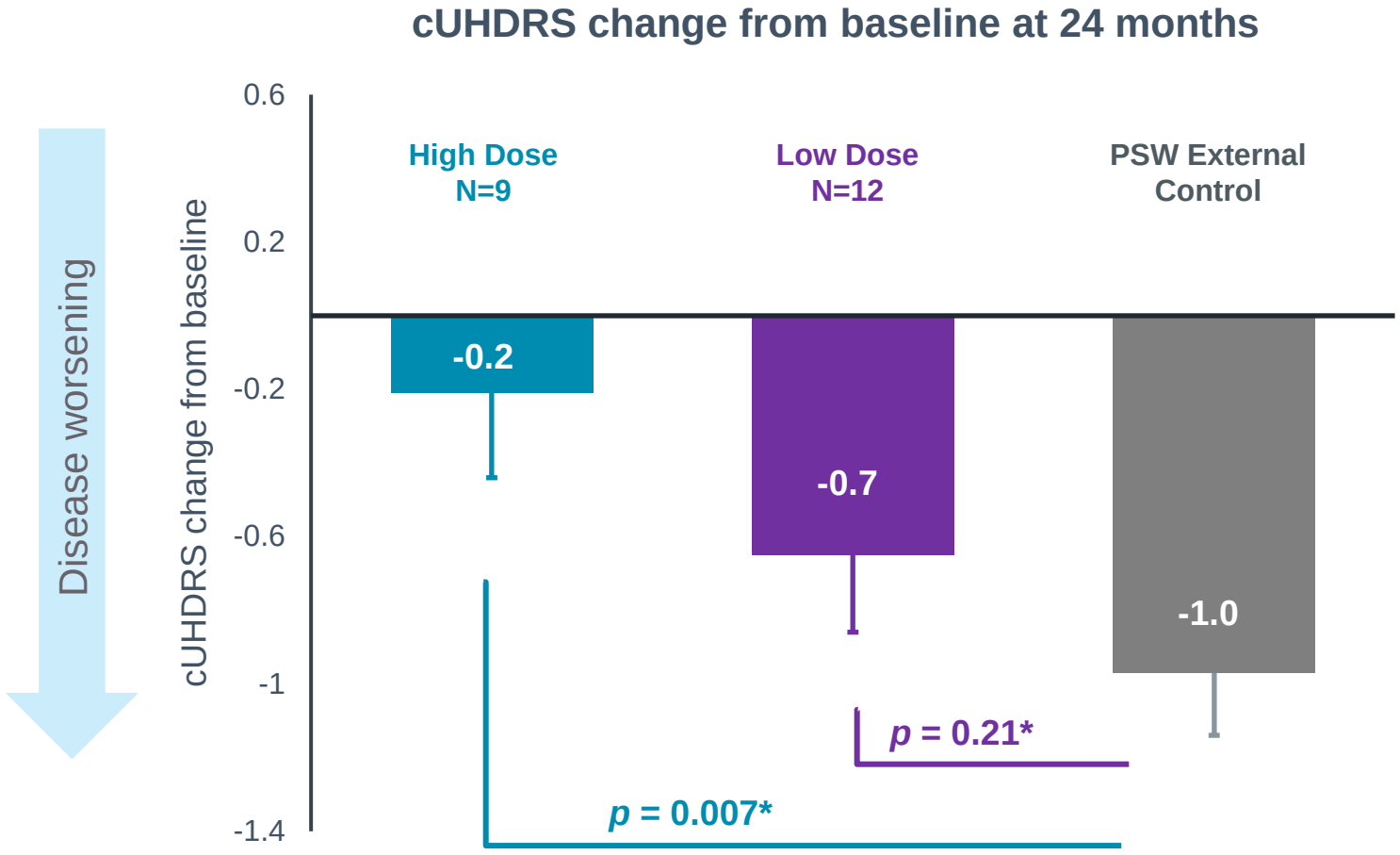
AMT-130 high-dose **significantly reduced disease progression by 80% based on cUHDRS at 24 months** compared to natural history. (95% CI [0.2, 1.3])

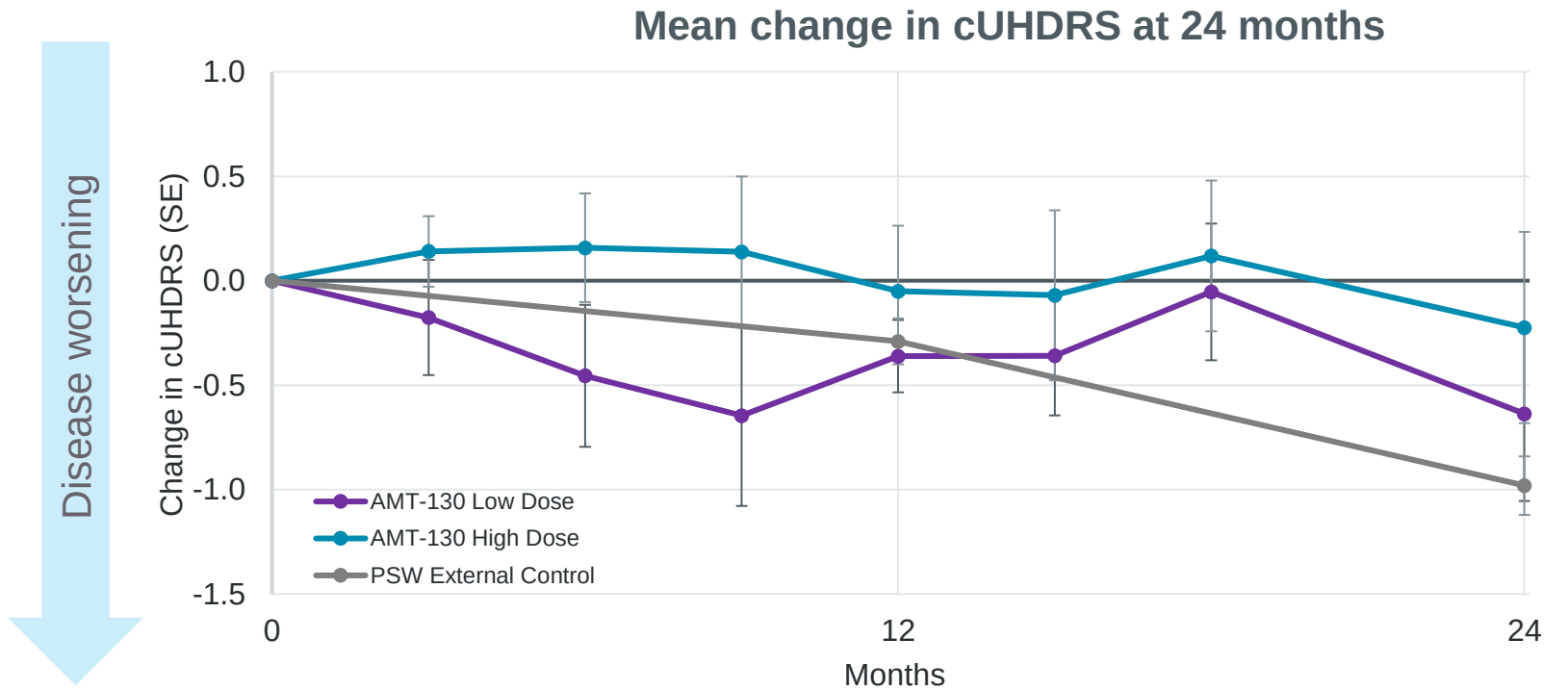
The difference between low- and high-dose AMT-130 is **evidence of a dose-dependent response.**



Abbreviations: cUHDRS, composite Unified Huntington's Disease Rating Scale; SE, standard error.
References: Data on file. June 2024.
* All p-values are nominal and unadjusted. Statistical comparisons of patients treated with AMT-130 to the propensity score-weighted external control were conducted on a post-hoc basis.

High-dose of AMT-130 preserved function through 24 months

Trends through 24 months indicate **sustained, dose-dependent slowing of disease progression as measured by cUHDRS** compared to the propensity score-weighted external control.

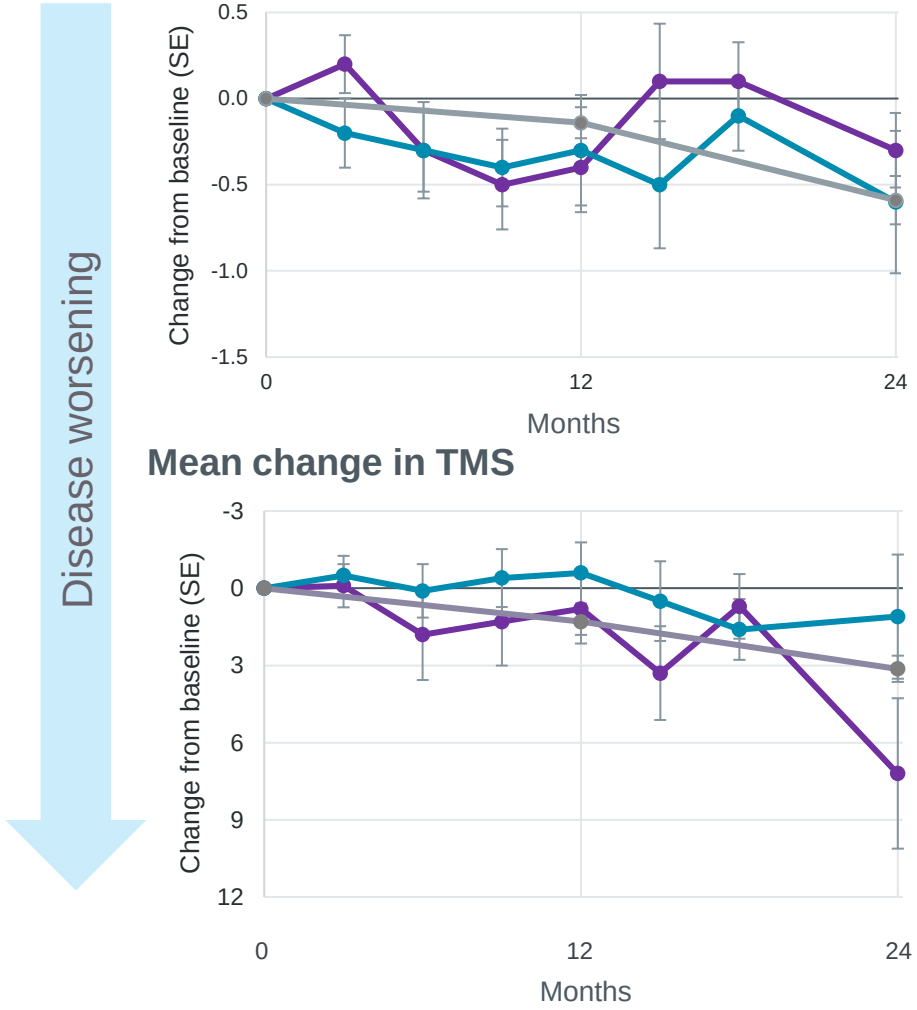


Patients	Base	3M	6M	9M	12M	15M	18M		24M
High Dose	17	17	17	17	14	13	12		9
Low Dose	12	12	12	12	12	12	12		12

Abbreviations: cUHDRS, composite Unified Huntington's Disease Rating Scale.
References: Data on file, June 2024.

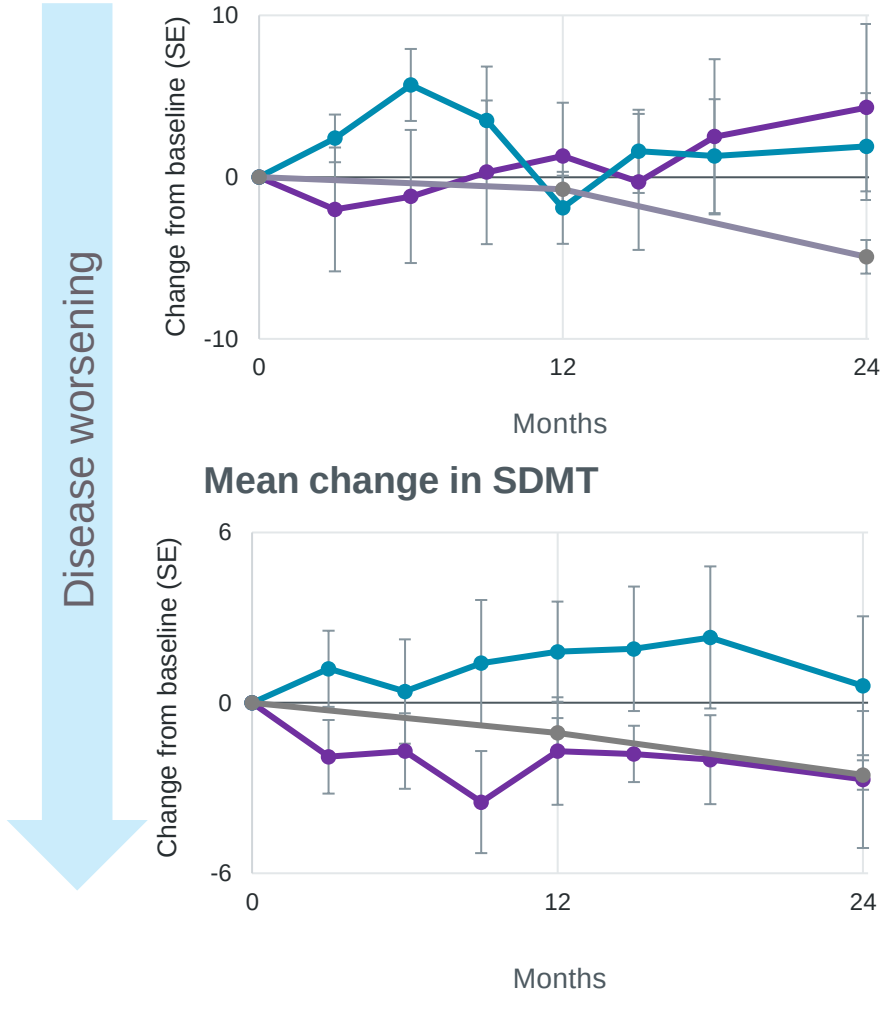
High-dose AMT-130 was favorable to external control across most individual components of cUHDRS

Mean change in TFC

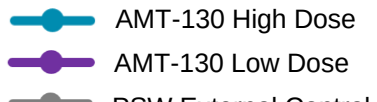


Mean change in TMS

Mean change in SWRT



Mean change in SDMT



Abbreviations: : SDMT, Symbol Digit Reading Modalities Test; SWT, Stroop Word Reading Test; TFC, Total Function Capacity; TMS, Total Motor Score.
References: Data on file. June 2024.

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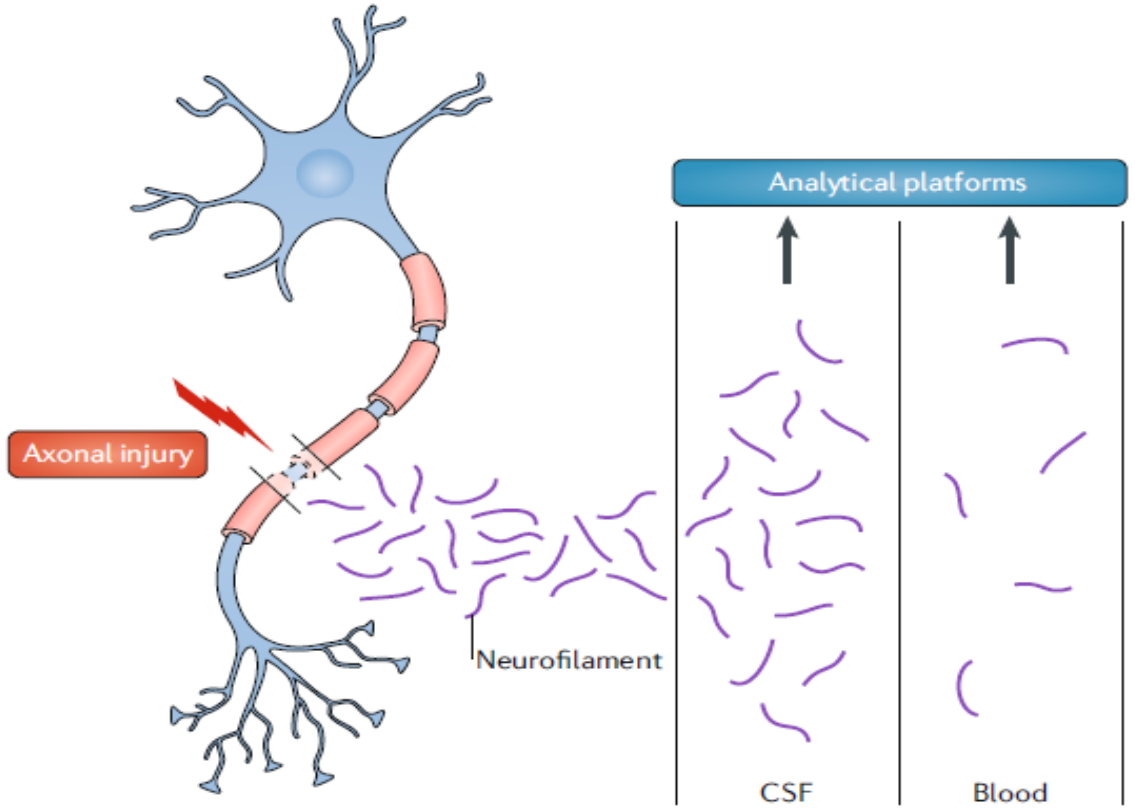
Neurodegeneration

Neurofilament light chain (NfL) is a key biomarker in Huntington's Disease

NfL is **released when neurons are damaged** and is an **important measure of neurodegeneration** in HD

NfL reduction was **used as a surrogate biomarker for accelerated approval in ALS**



Neurofilament release after axonal damage.

Abbreviations: ALS, amyotrophic lateral sclerosis; NfL, neurofilament light chain**;** HD, Huntington's Disease. **References:** Rodrigues FB, *et al. Sci Transl Med*. 2021; 12(574). Khalil M, *et al. Nat Rev Neurol.* 2018; 14: 577-89; Kalm M *et al. Brain Res* 2017; 1668: 12-19. Data on file. June 2024.

AMT-130 demonstrated reduction in a key measure of neurodegeneration at 24 months

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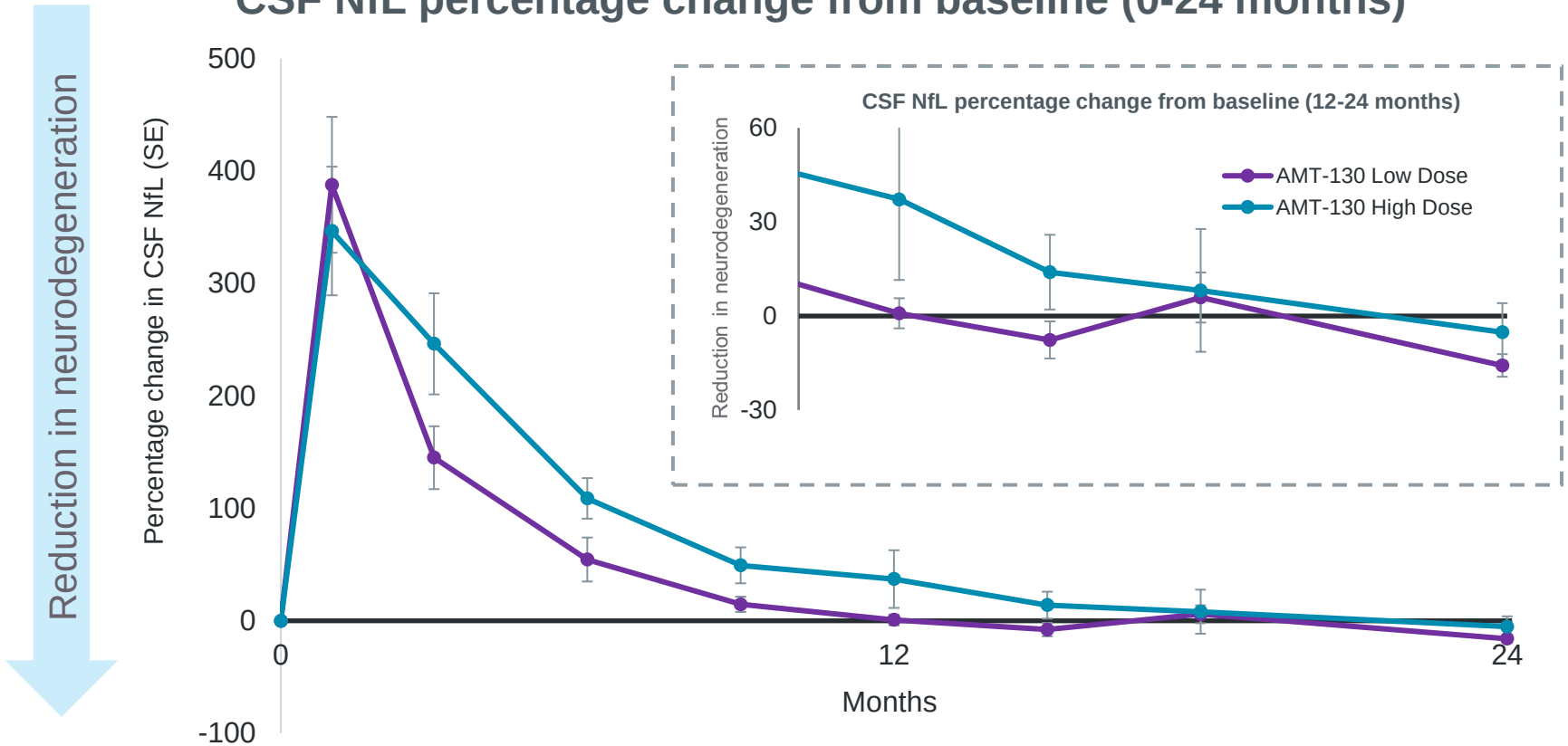
Mean CSF NfL levels at both doses were below baseline at 24 months, indicating **long-term reductions in neurodegeneration.**



Patients	Base	1M	3M	6M	9M	12M	15M	18M		24M
High-Dose	17	17	16	16	15	11	11	12		9
Low-Dose	12	12	11	12	12	12	12	12		12

Abbreviations: CSF, Cerebrospinal fluid; NfL Neurofilament light chain; Standard Error (SE).
References: Data on file. June 2024.

NfL increases over time mark proliferation of neurodegeneration in Huntington's Disease

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An independent study has confirmed a **strong association between CSF NfL levels and the clinical severity of HD.**

The study demonstrated early-manifest HD patients will experience **increases in CSF NfL of ~10% to 15% per year.**

Recent data from HD-CSF study where CSF NfL levels were measured in 71 patients over a two-year period showed an increase over time and a sigmoid trajectory with age.

Abbreviations: CSF, cerebrospinal fluid; NfL, neurofilament light chain; HD, Huntington's Disease.
References: Rodrigues et al. *Sci Transl Med* 2021, Ed Wild, personal communication

The relationship between NfL and age in HD

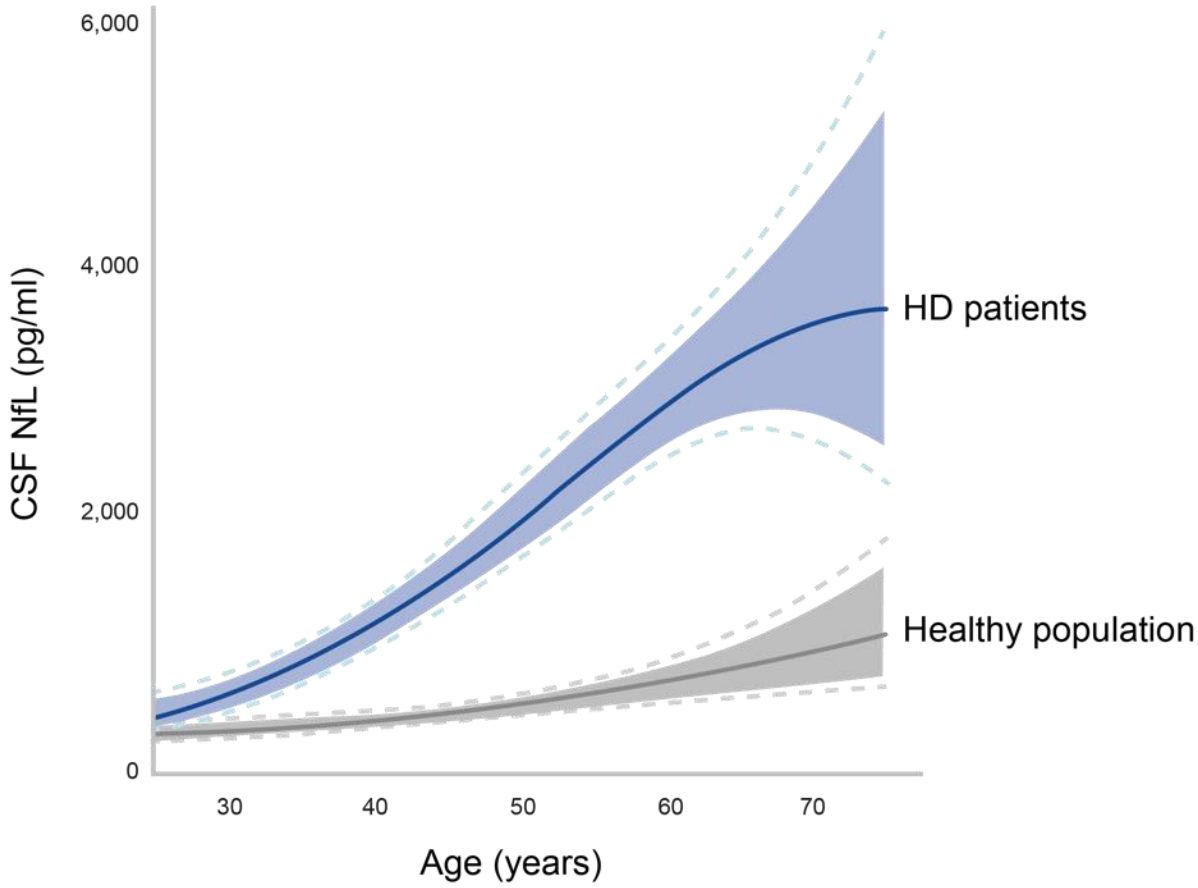

Image reproduced and modified from Rodrigues et al. Sci. Transl. Med. 2021

AMT-130 demonstrated statistically significant reduction of CSF NfL at 24 months

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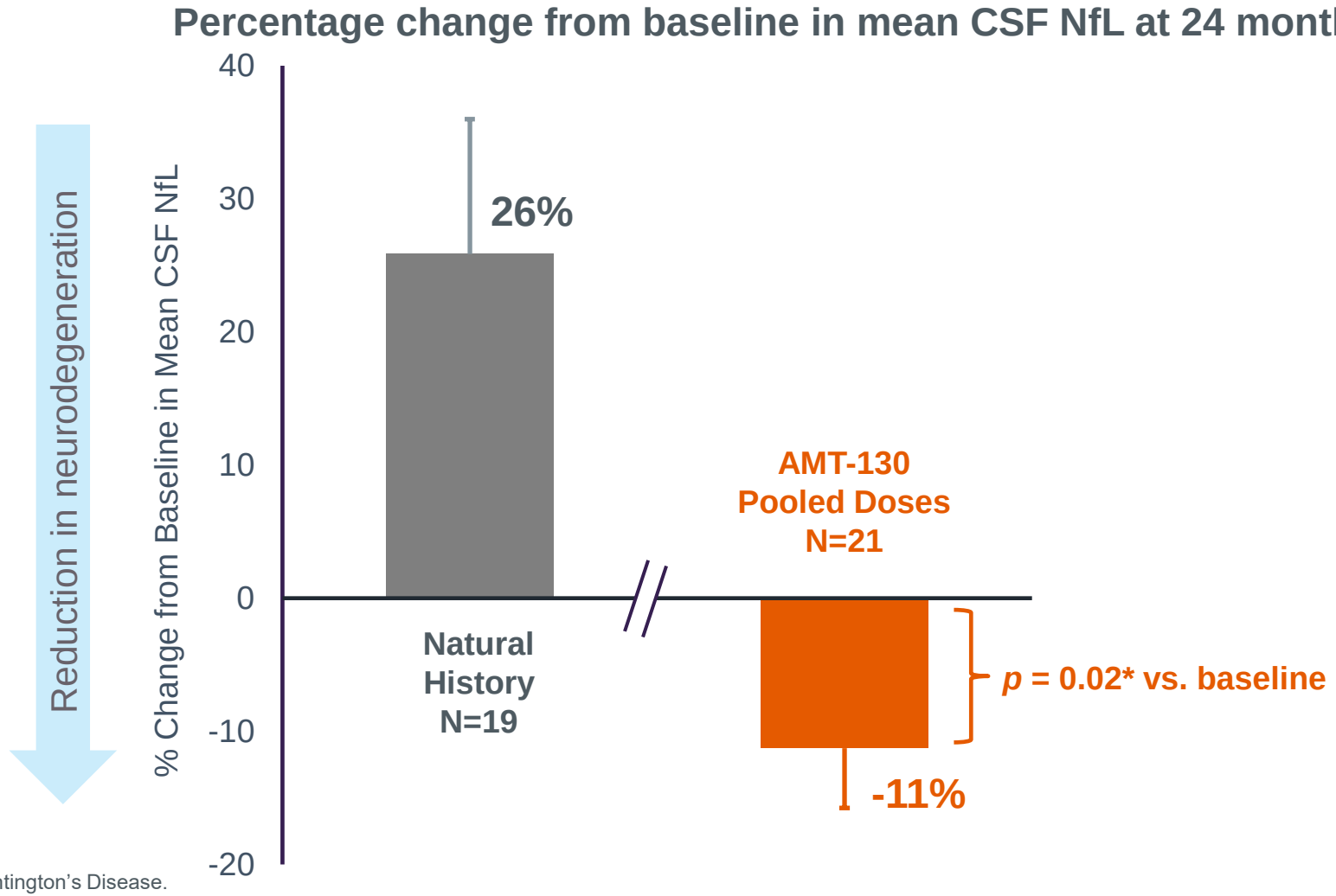
AMT-130 **significantly reduced CSF NfL at 24 months vs. baseline.**

(95% CI [-20.6 %, –1.9%])

Natural history cohort consisted of all patients from HD-CSF study who met the AMT-130 inclusion criteria (n=19).



Abbreviations: CSF, cerebrospinal fluid; NfL, neurofilament light chain; HD, Huntington's Disease.
References: Rodrigues FB, *et al. Sci Transl Med*. 2021; 12(574). Data on file. June 2024.
* All p-values are nominal and unadjusted.

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Safety & Tolerability

AMT-130 remained generally well-tolerated, with a manageable safety profile at both doses, no new drug related SAEs reported

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	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	6	30.0
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	0	0.0	0	0.0	4*	20.0
Most Common TEAEs (≥30% in at least one group)						
Procedural headache	5	50.0	4	30.8	10	50.0
Procedural complication	4	40.0	4	30.8	5	25.0
Headache	3	30.0	3	23.1	8	40.0
Post lumbar puncture syndrome	6	60.0	2	15.4	6	30.0
Procedural pain	6	60.0	2	15.4	7	35.0

** 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 March 31, 2024; [&]Crossover patients included***

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Conclusions & Next Steps

AMT-130: promising trends observed in clinical assessments and continued decline of CSF NfL

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- AMT-130 continues to be generally well-tolerated, with a manageable safety profile at both doses
- Patients treated with AMT-130 showed signs of preserved neurologic function relative to baseline, and emerging, statistically significant evidence of potential therapeutic benefit relative to a matched natural history cohort
- CSF NfL levels after two years of treatment were statistically significantly lower than baseline in contrast to an expected increase observed over the same period in natural history patients
- Totality of evidence suggests that AMT-130 reduces the underlying neurodegeneration and slows the rate of progression of disease

uniQure Next steps

RMAT designation offers all the benefits of the Fast Track and Breakthrough Therapy designation programs, **allowing for close collaboration with the FDA.**

We will work with the FDA to continue the development of AMT-130 to ensure patients receive the treatment they need.

Next steps:

- Continue to **interact with regulatory agencies under RMAT to define the registrational pathway** (H2 2024)
- **Complete enrollment of Cohort 3** to investigate the effects of immune suppression on perioperative safety (Q4 2024)
- **Provide initial safety data from Cohort 3** (1H 2025)
- **Provide updates on the Phase I/II trials** with up to three years of data (mid-2025)

Abbreviations: FDA, Food & Drug Administration; RMAT, regenerative medicine advanced therapy.

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Key Opinion Leader Perspective

Victor Sung, M.D.
University of Alabama at Birmingham (UAB)

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Research Analyst Questions

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Closing Remarks

Matt Kapusta
Chief Executive Officer

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About the Propensity Score-Weighting Methodology

Propensity score-weighting (PSW) is an established, robust statistical method used to reduce selection bias and confounding variables when comparing an external control to a treatment cohort

Key steps in the analysis include:

1. **Select Covariates:** Identify variables at baseline that are disease prognostic factors. Imbalances in these factors at baseline can impact the interpretation of outcomes.

2. **Calculate Propensity Scores (PS)**: Use a logistic regression model with the selected covariates to estimate propensity scores, which quantify the baseline similarity of individual subjects in the natural history cohort compared to the treatment group.

3. **Weight External Control**: The weight of treated subjects is 1.0; The weight of patients in the external control is calculated as PS/(1-PS).

4. **Evaluate Balance:** Assess covariates between the treatment cohort and the external control to ensure effective balancing of baseline characteristics.

(1) Prognostic factors include CAG (cytosine-adenine-guanine) repeats; CAP (CAG-Age-Product) Score; cUHDRS (composite Unified Huntington's Disease Rating Scale); DCL (diagnostic confidence level); PIN Score (Prognostic Index), and TFC (Total Function Capacity).

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References and abbreviations

ALS, amyotrophic lateral sclerosis;

CSF, cerebrospinal fluid;

cUHDRS, composite Unified Huntington’s Disease Rating Scale;

FDA, Food & Drug Administration;

HD, Huntington’s Disease;

NfL, neurofilament light chain;

NHC, natural history cohort;

RMAT, regenerative medicine advanced therapy;

SE, standard error;

SDMT, Symbol Digit Modalities Test;

SWT, Stroop Word Reading Test;

TFC, Total Function Capacity;

TMS, Total Motor Score;