Top-line IONIS-HTT$_{Rx}$ (RG6042) Phase 1/2 Study Results

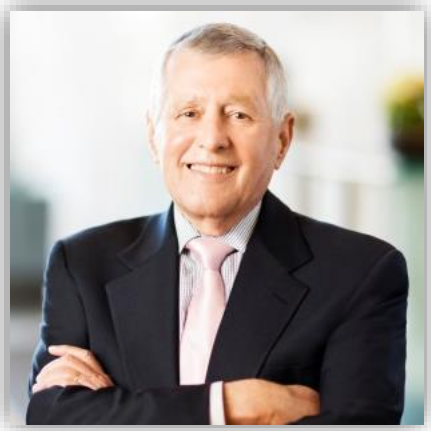
Conference Call and Webcast

March 2, 2018

IONIS™ PHARMACEUTICALS

Today's Presenters

Stanley Crooke, M.D., Ph.D.
CEO and Chairman
Ionis Pharmaceuticals



Frank Bennett, Ph.D.
Senior VP of Research
Franchise Leader for Neurological Programs
Ionis Pharmaceuticals

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Clinical Science Leader of Product Development Neuroscience
Hoffmann-La Roche Pharmaceuticals

Forward Looking Statements

This presentation includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of IONIS-HTT$_{Rx}$ and other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of SPINRAZA, inotersen, volanesorsen and other of Ionis' drugs in development is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2017, which is on file with the SEC. Copies of this and other documents are available from the Company.

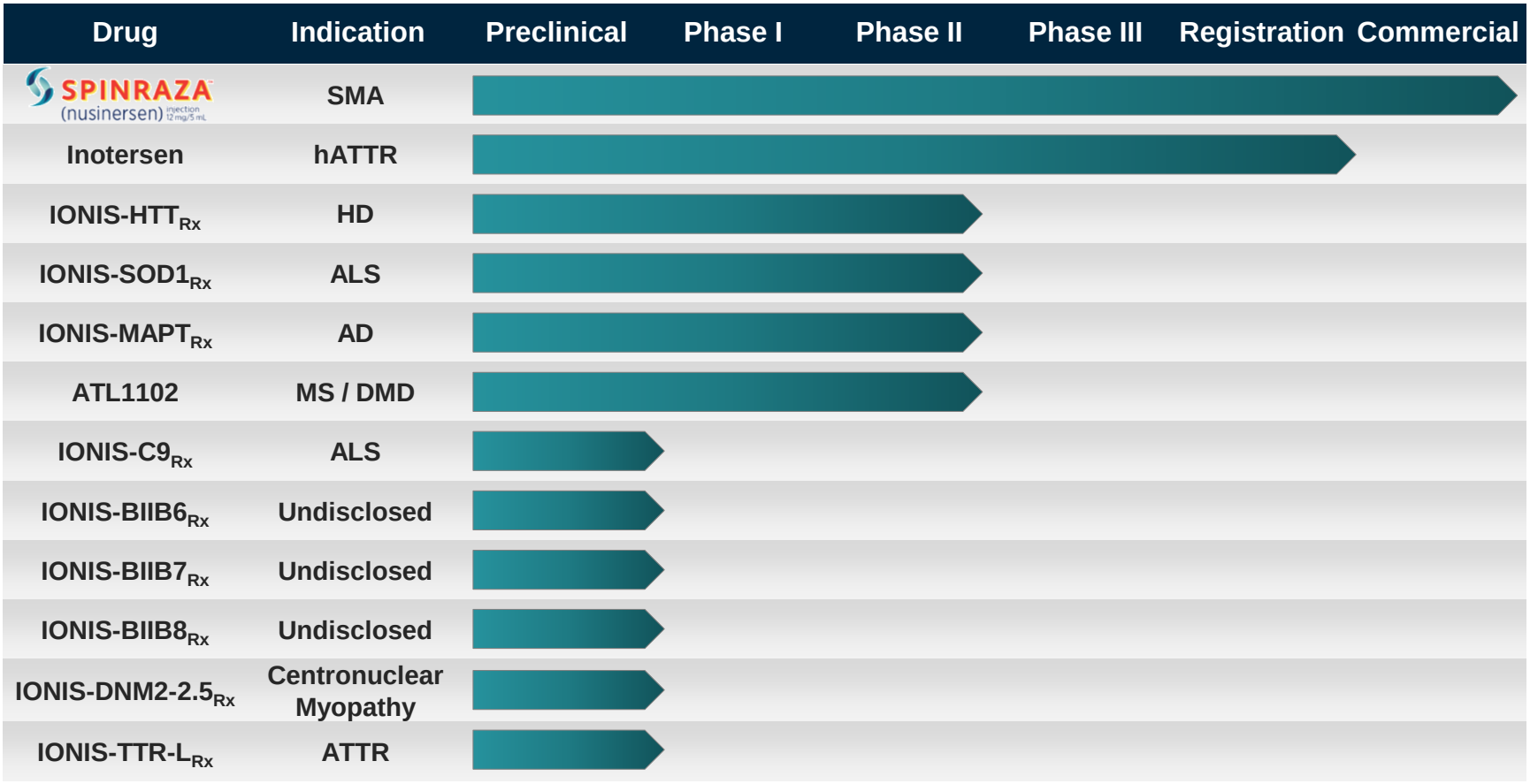
In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries. Ionis Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Ionis Pharmaceuticals, Inc. SPINRAZA® is a registered trademark of Biogen.

Webcast Agenda

Topic	Speaker
- **Welcome and Introductions**	Stanley Crooke, M.D., Ph.D.
- **Huntington's Disease Background** - **Preclinical Data**	Frank Bennett, Ph.D.
- **Phase 1/2 Clinical Data**	Sarah Tabrizi, M.D., Ph.D., FMedSci
- **Goals of Clinical Efficacy Testing** - **Next Steps**	Scott Schobel, M.D., M.Sc., Roche
- **Conclusion and Q&A**	Stanley Crooke, M.D., Ph.D.

Ionis is Emerging as a Leader in Neurological Diseases

Our antisense technology is well-suited to treat a broad range of diseases, including neurological and neurodegenerative diseases



With more than 20 wholly owned and partnered drug discovery programs

For Alzheimer's, Parkinson's, ALS, pain and multiple rare neuro diseases

IONIS-HTT$_{Rx}$ (RG6042): First and Only Drug to Demonstrate Robust, Dose-dependent Reductions of mHTT in HD Patients

Up to ~60% (~40% mean) reduction of mHTT in CSF after three months of treatment, with reductions continuing

We expect the planned dosing regimen for IONIS-HTT$_{Rx}$ to result in optimal target reduction

HD is a significant area of unmet need with 30,000 patients diagnosed in the U.S. and 200,000 at-risk

Initial data supports the potential of IONIS-HTT$_{Rx}$ to safely treat all patients with Huntington's Disease (HD)

Roche and Ionis are working to quickly advance IONIS-HTT$_{Rx}$ to a pivotal clinical efficacy study

What We Mean by Optimal Target Reduction

We expect the planned dosing regimen for IONIS-HTT$_{Rx}$ to result in optimal target reduction

- Our data support that a 40-60% reduction of mutant huntingtin protein (mHTT) in CSF will translate to approximately 55-85% reduction in the cortex
- Disease modification in animal models of HD occurs at 30-50% mHTT reduction in the cortex
- The mHTT reduction we observe in the Phase 1/2 study exceeds the reduction that produced disease modification in animal models of HD

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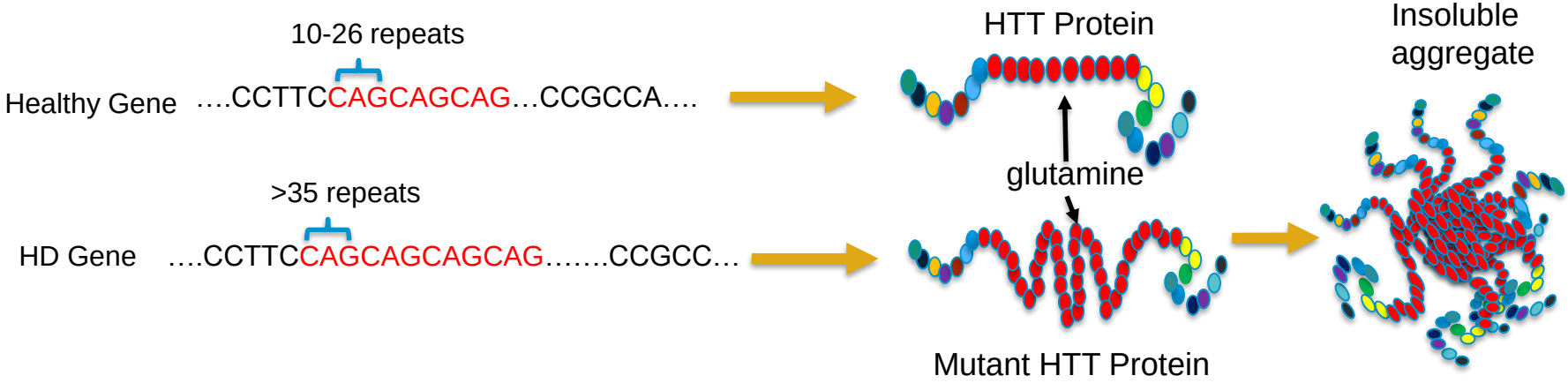
Huntington's Disease (HD)

A rare, genetic, fatal neurodegenerative disease

HD is…

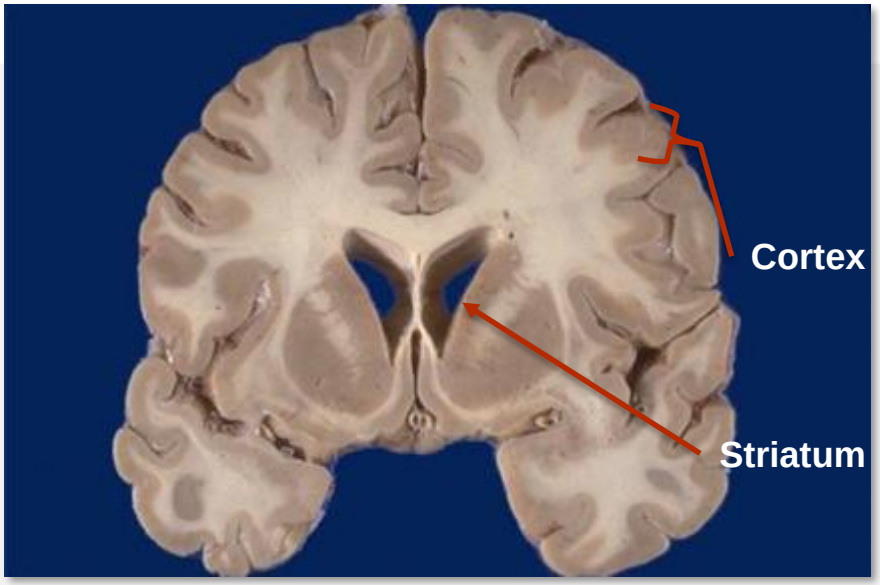
- **Fatal** – motor, cognitive and psychiatric symptoms, leading to overall decline and mortality 15-20 years post symptom onset
- **Hereditary** – caused by a toxic gain-of-function triplet repeat (CAG) expansion in the huntingtin gene, children of gene carriers have 50% chance of inheritance
- **Widespread** – approximately 3-10 per 100,000 people worldwide are affected by HD; about 30,000 symptomatic patients in the U.S.



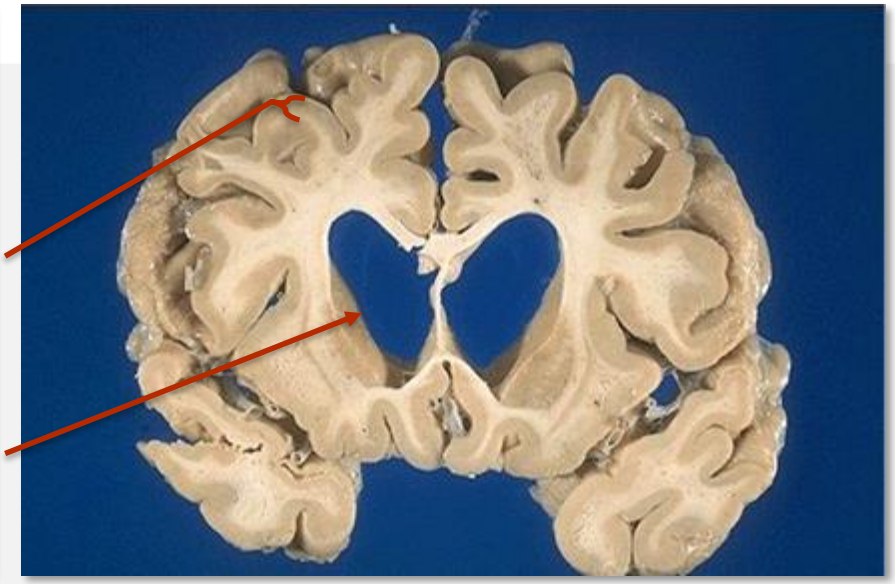
HD is a Whole Brain Disease

Neuronal degeneration and severe atrophy observed in multiple brain regions

Healthy Brain



Huntington's Brain

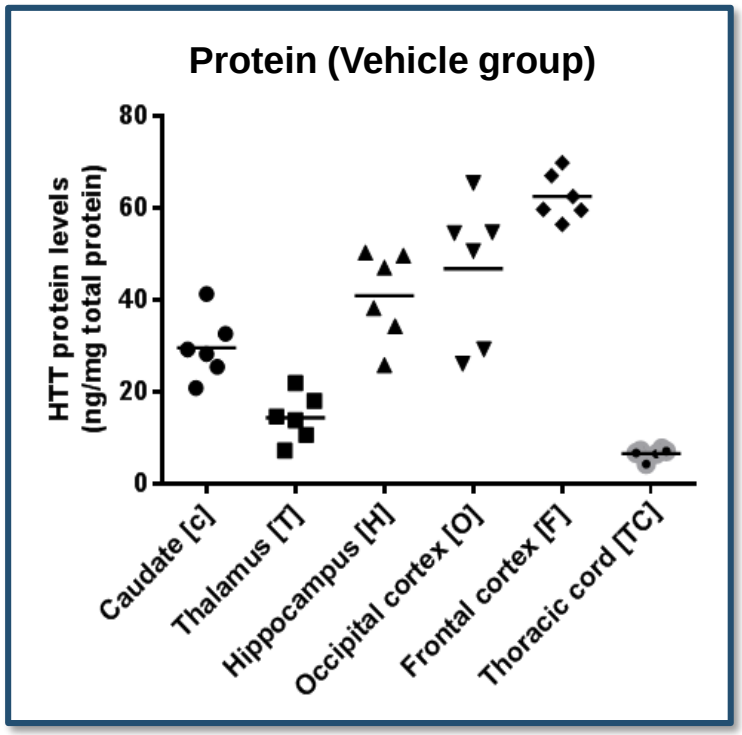


- Continual loss of neurons throughout the brain
- At autopsy, greatly reduced brain size (~30%; 400-600 gm loss)
- Not just a striatal disease (healthy striatum is only 20 to 30 gm)

Several Publications Highlight the Importance of Inhibiting mHTT in Cortical Neurons

mHTT lowering in cortical neurons benefits striatal neurons

The cortex has highest concentration of HTT protein in the brain



Neurobiology of Disease

Cortical efferents lacking mutant huntingtin improve striatal neuronal activity and behavior in a conditional mouse model of Huntington's disease[1]

nature medicine

Neuronal targets for reducing mutant huntingtin expression to ameliorate disease in a mouse model of Huntington's disease[2]

Molecular Neurodegeneration

Pathological cell-cell interactions are necessary for striatal pathogenesis in a conditional mouse model of Huntington's disease[3]

mHTT = mutant huntingtin protein

1. *Estrada-Sánchez, A. M. et al. (2015) J Neurosci 35, 4440–4451.*
2. *Wang, N. et al. (2014) Nature Medicine 20, 536–541.*
3. *Gu, X. et al. (2007) Mol Neurodegener 2, 8.*

Key Questions Addressed in the Development of IONIS-HTT$_{Rx}$ for Patients with HD

- Can Generation 2+ antisense drugs target HTT in the brain?
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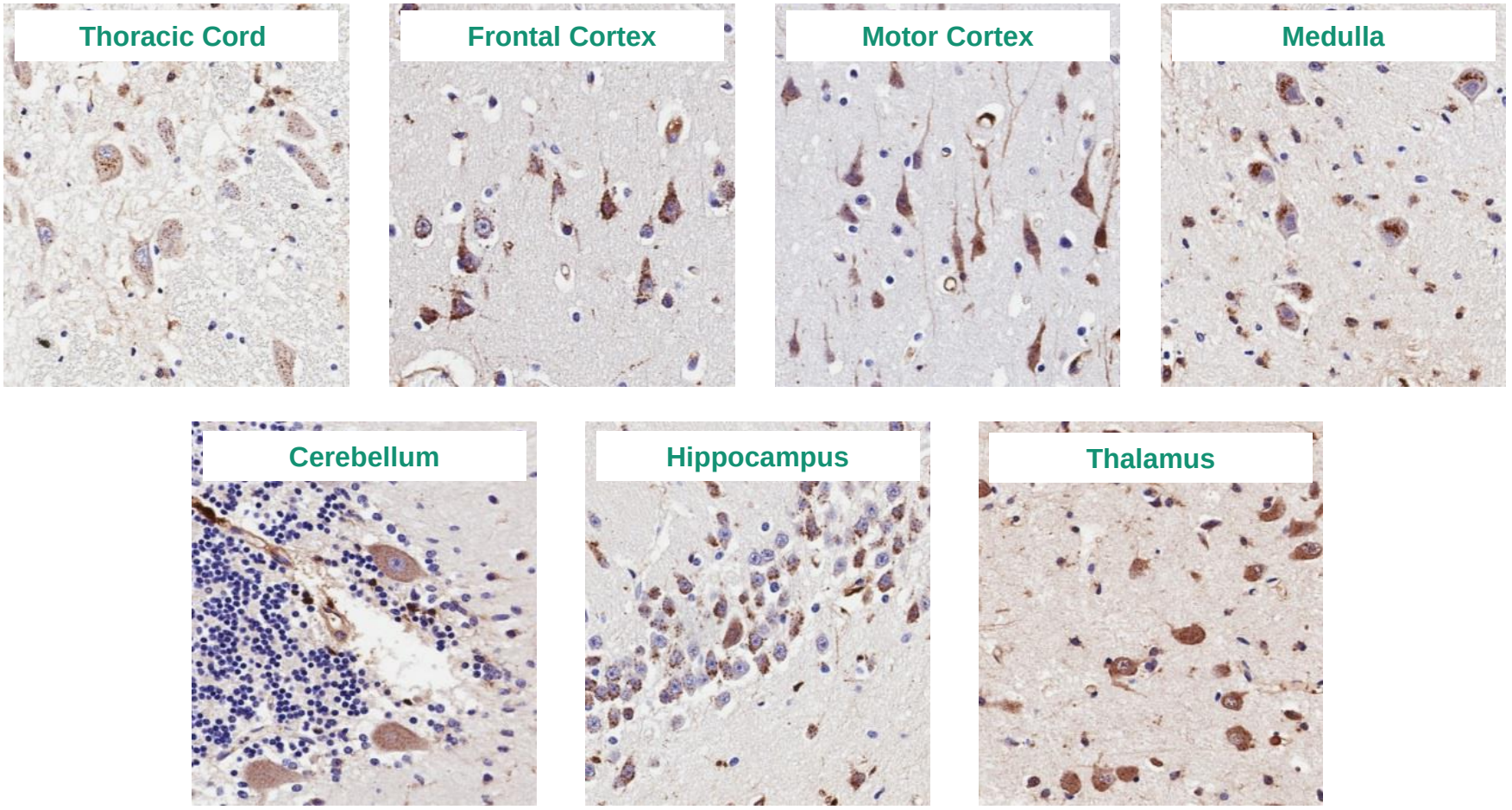
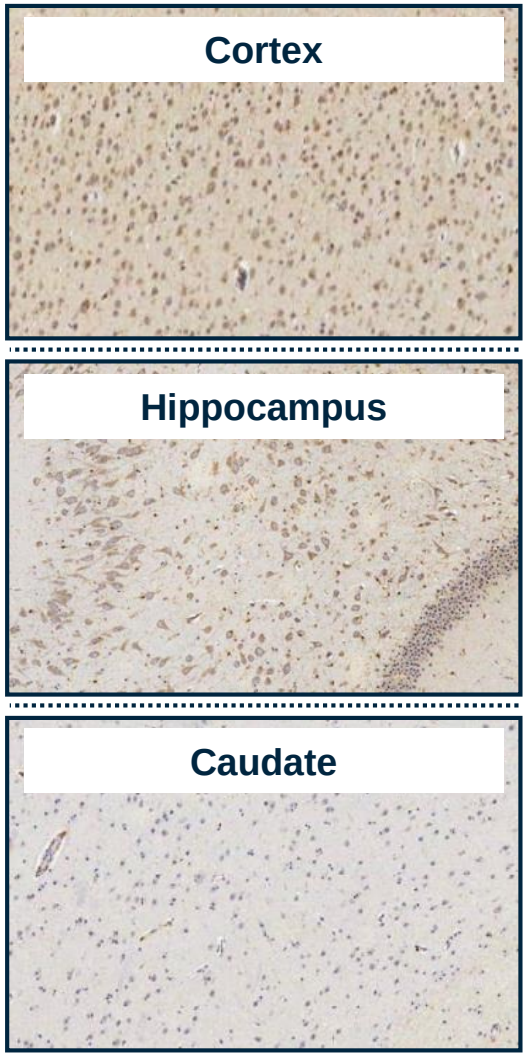
Antisense Drugs Distribute Throughout the CNS in Humans Following Intrathecal (IT) Dosing

Brain Tissue Samples of SPINRAZA-treated Infants with Spinal Muscular Atrophy

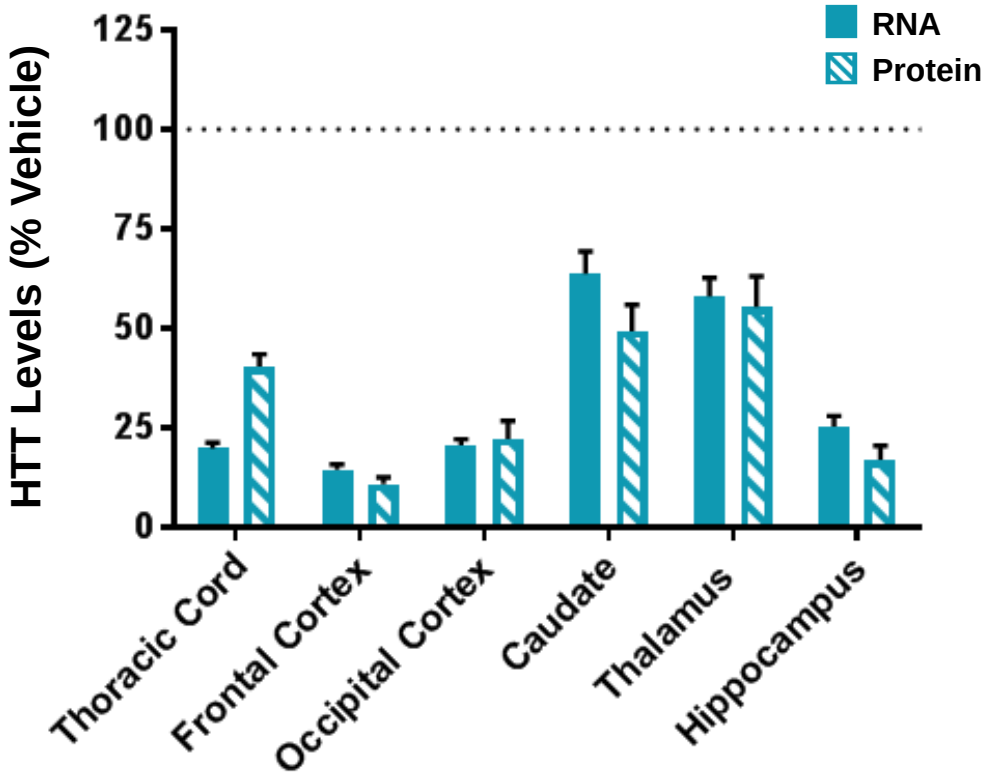


Finkel et al, Lancet 2017 *Note: Brown staining indicates SPINRAZA in cells*

HTT-targeting Antisense Drug Distributes Broadly and Substantially Reduces HTT Throughout the Brain in Non-human Primates Following IT Dosing



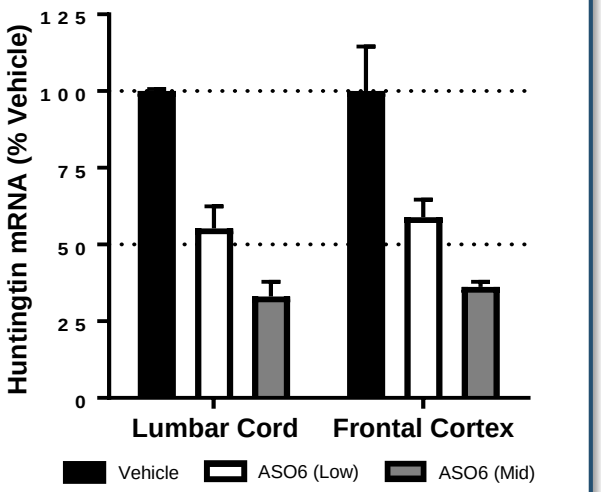
HTT RNA and Protein Reduction Throughout NHP Brain



Note: Brown staining indicates HTT-targeting antisense drug in cells; Non-human primate (NHP) dosed intrathecally 4x at once monthly intervals

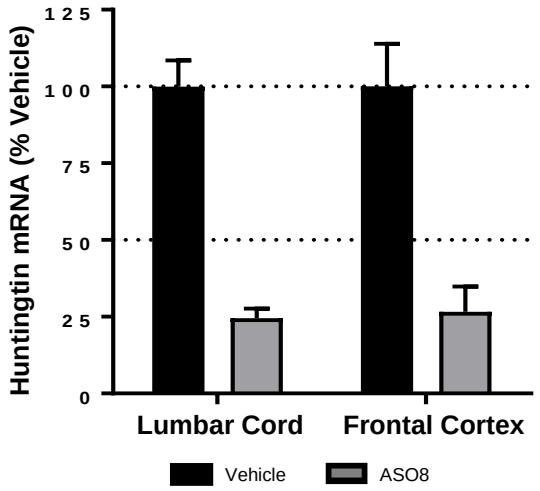
HTT-targeting Drug Distribution and Activity is Similar in Spinal Cord and Cortex in Multiple Large Animal Species With IT Dosing

Non-human Primate



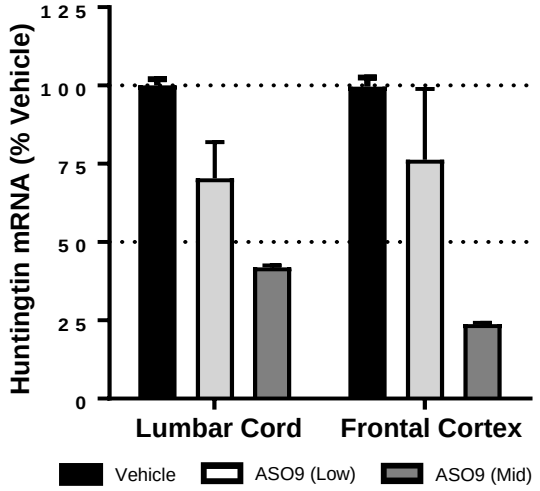
Yucatan Pig

(Spinal cord 51.2+/-3 cm)



Large Mongrel Dogs

(16.5+/-2.6 kg)



IT administration of antisense drugs results in broad distribution to spinal cord and brain tissue

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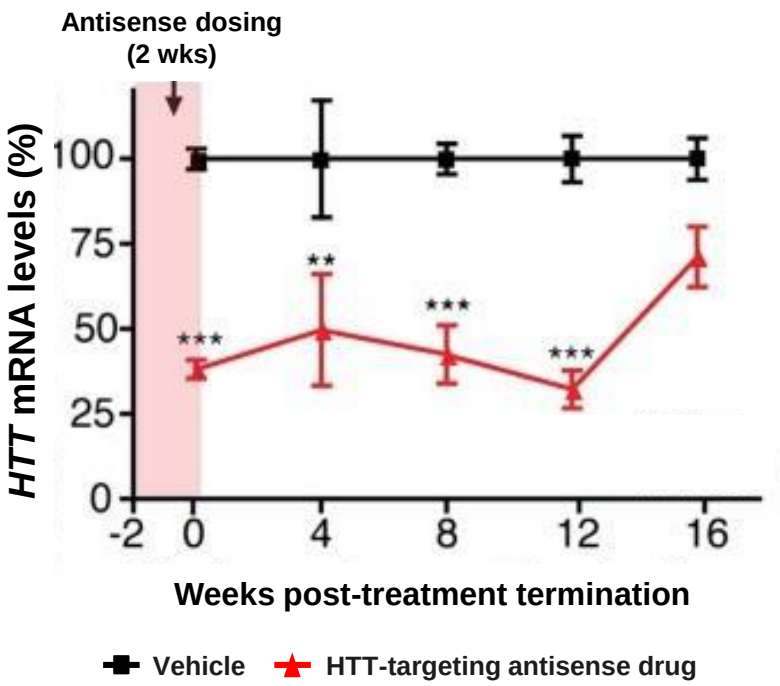
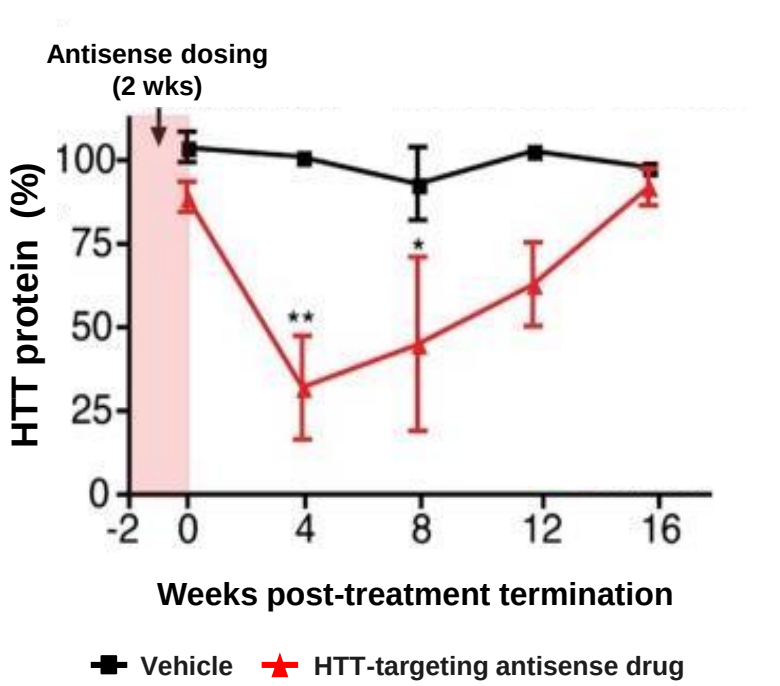
Human HTT-targeting Antisense Drugs Produced a Durable Reduction of Huntingtin mRNA and Protein in a Transgenic Mouse Model+ of HD

Sustained Reduction in Huntingtin mRNA



Sustained Reduction in Huntingtin Protein



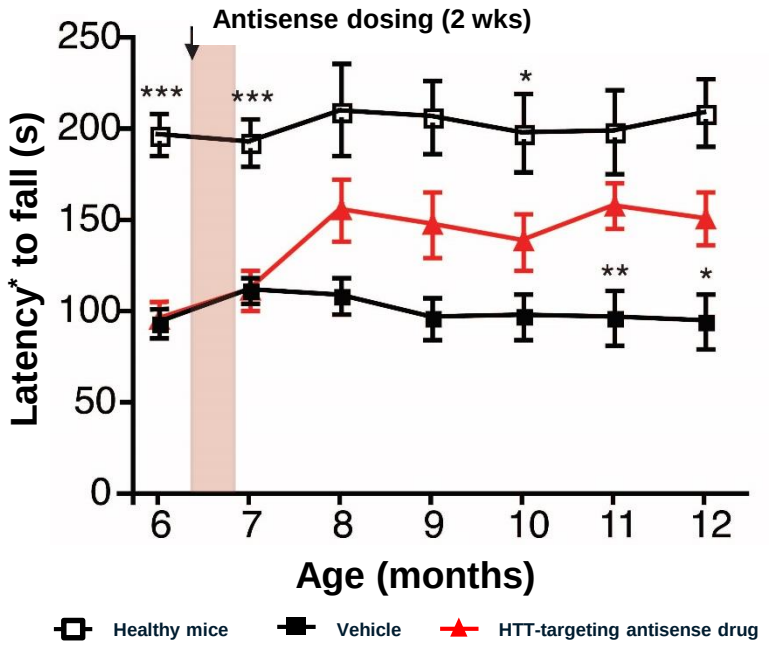
**P < 0.05, **P < 0.01, and ***P < 0.001*

+*The animal model used is a BAC-HD transgenic mouse*

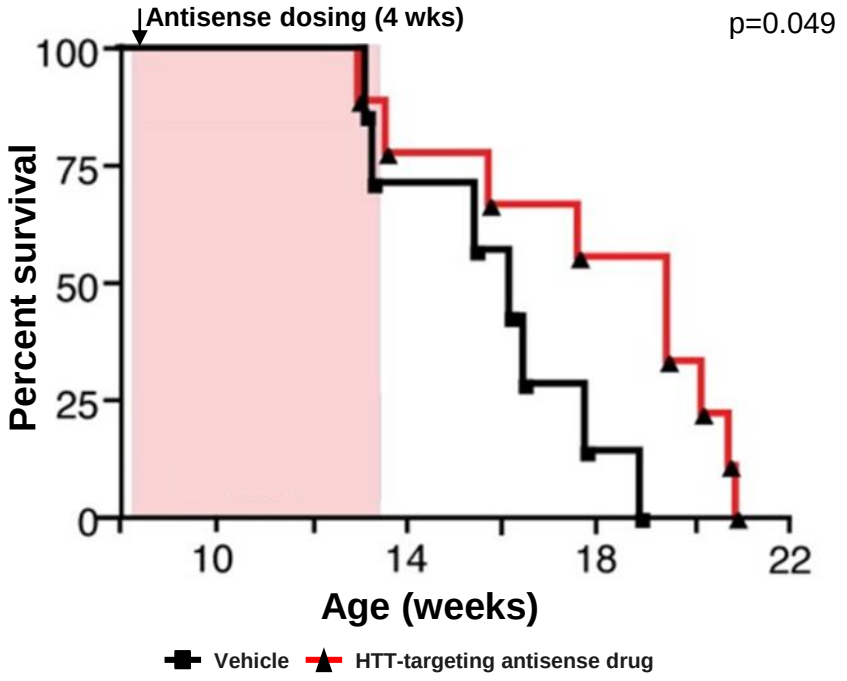
1. Kordasiewicz et al. (2012) Neuron. 74: 1031-1044.

HTT-targeting Antisense Drugs Improve Motor Function and Prolong Survival in Mouse Models of HD

Improved Motor Performance in BAC-HD Mice (rotarod test)



Prolonged Survival in R6/2 Mice



*P < 0.05, **P < 0.01, and ***P < 0.001

+Latency to fall, or longer time to fall off the spinning rotarod test apparatus. Longer latency suggests better motor performance.

Approximately 50% HTT reduction in brain tissue correlated with improved motor performance and prolonged survival

1. Kordasiewicz et al. (2012) Neuron. 74: 1031-1044.

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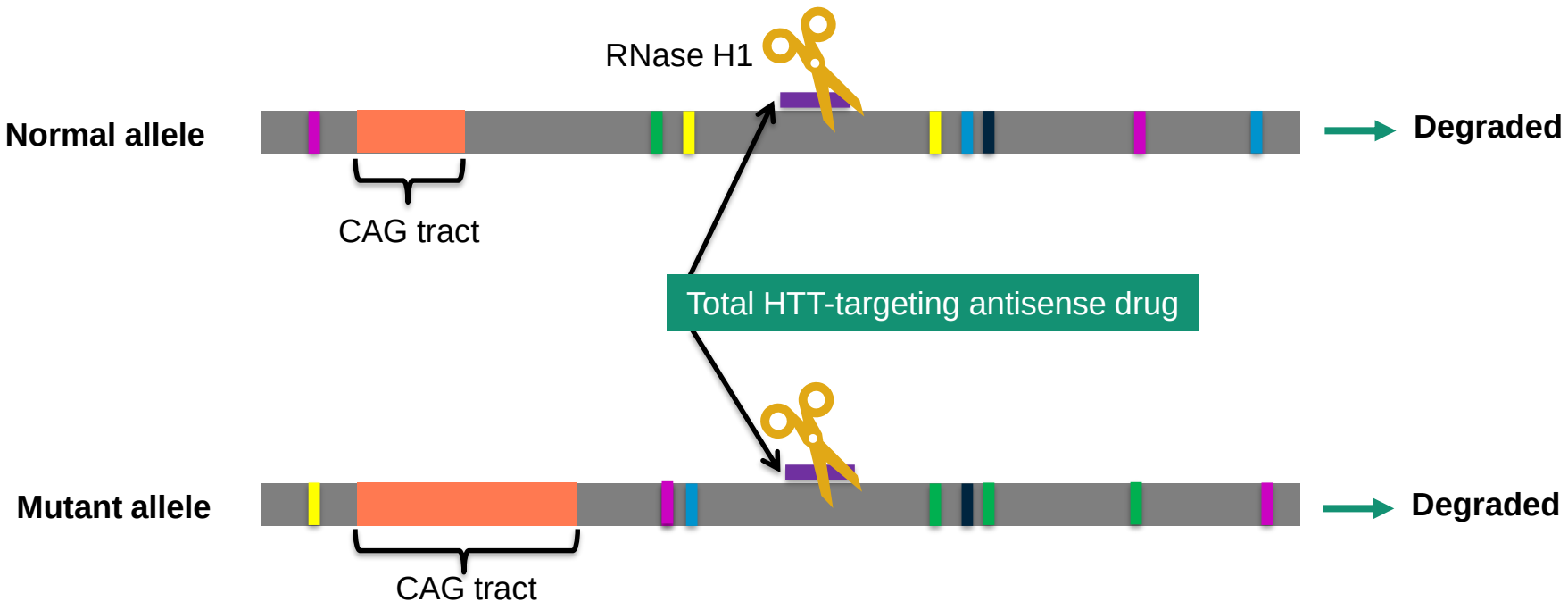
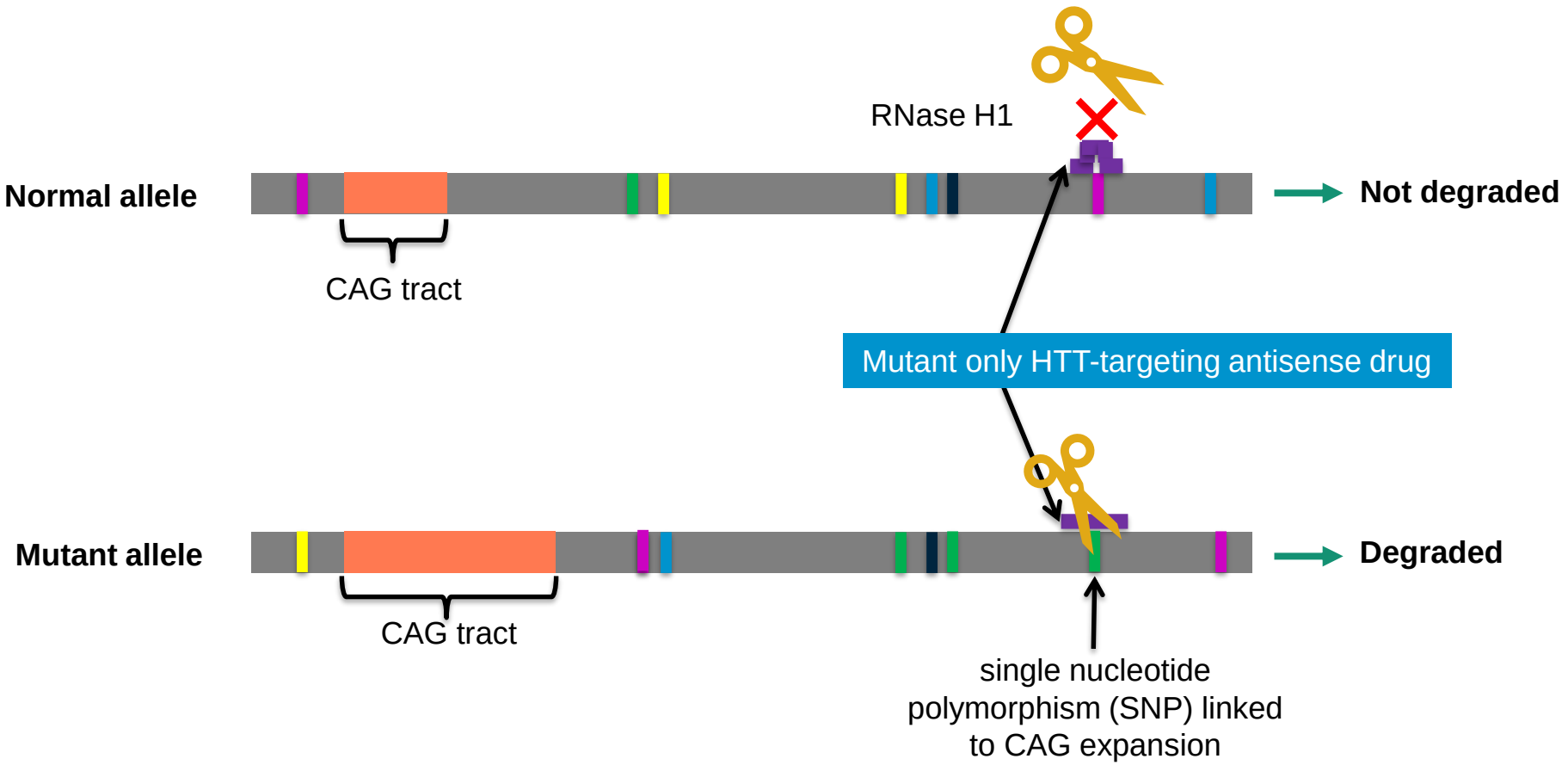
Antisense Approach Targeting Total HTT



Antisense Approach Targeting Only Mutant HTT



Potential Advantages and Disadvantages of Approaches for Targeting mHTT

	Total HTT-targeting Drug	Mutant Only HTT-targeting Drug
Potential Advantages	▪ Address all HD patients ▪ More robust activity achieved with more sequence to target	▪ Preferential reduction of the CAG-expanded huntingtin protein
Potential Disadvantages	▪ Reduces both alleles ▪ Reduction of normal HTT is safe in adult animals but required for early development	▪ Each antisense drug is only useful for a subset of HD patients ▪ ~5 drugs needed to treat all HD patients ▪ Restricted binding sites reduce potency and ability to identify safest drug ▪ Companion diagnostics challenging

HTT-targeting Strategies – Ionis Publications

Carroll et al. Mol. Therapy, 2011
Gagnon et al. Biochemistry, 2010
Hu et al. NAR, 2014
Kordasiewicz et al. Neuron, 2012
Stanek et al. J. Huntington Disease, 2013
Ostergaard et al. NAR, 2013
Ostergaard et al. NAT, 2015
Ostergaard et al., Mol. Ther. 2017
Skotte et al. PLOS One, 2014
Southwell et al. Mol. Therap. 2014
Southwell et al. Human Mol. Gene 2017
Yu et al. Cell, 2012

Multiple Preclinical Studies Support Targeting Total HTT in Patients with HD

- Following careful review of the extensive preclinical data, we and our partner Roche decided to advance 1 drug into the clinic with the potential to treat all HD patients
  - HTT-targeting antisense drugs distribute to necessary regions and produce robust reductions in HTT mRNA protein after IT administration
  - Total HTT-targeting antisense drugs demonstrate more robust activity is achievable compared to mutant only approach
  - Total HTT-targeting antisense drugs exhibit good safety and tolerability profile in preclinical and clinical studies to date
  - Total HTT-targeting provides best approach for addressing all HD patients

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Comprehensive Preclinical Package Supports Targeting Total HTT in Patients with HD

- Data support a wide safety margin for dosing in the clinic
- No evidence of toxicity resulting from reduction of normal HTT in toxicology or safety pharmacology studies
  - 6-month non-human primate (3-month treatment and 3-month follow up)
  - 15-month non-human primate (9-month treatment and 6-month follow up)
  - 3-month mouse
  - Single-dose rat
- No genetic toxicity
- No reproductive toxicity

No safety issues with up to 80% reduction in total HTT in the NHP brain

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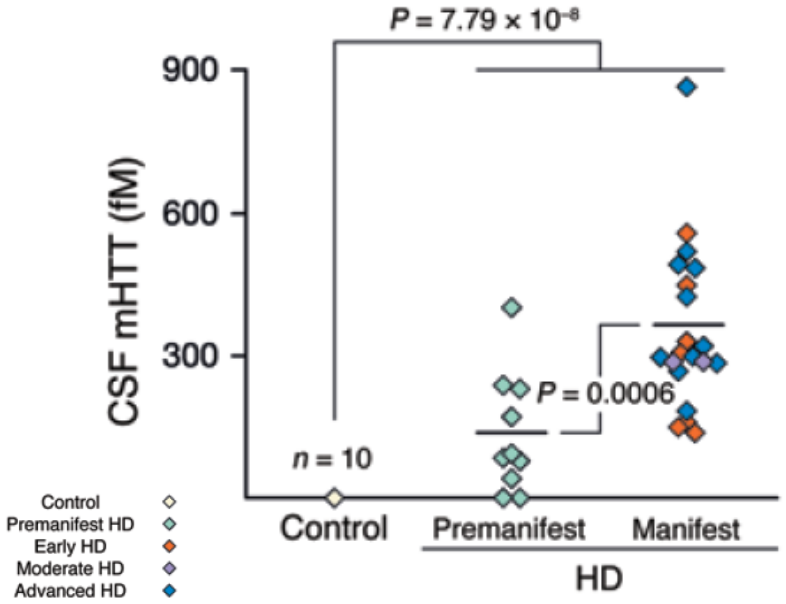
Sensitive and Reproducible Assay Developed to Detect mHTT in Cerebral Spinal Fluid (CSF) from Patients with HD

JCI The Journal of Clinical Investigation
Published by The American Society for Clinical Investigation | Founded 1908

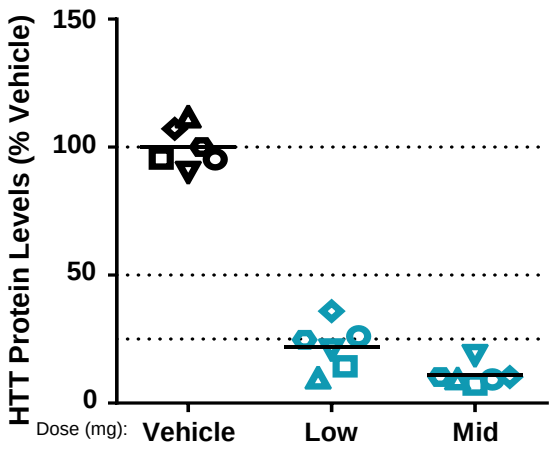
Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients

Edward J. Wild,[1] Roberto Boggio,[2] Douglas Langbehn,[3] Nicola Robertson,[1] Salman Haider,[1] James R.C. Miller,[1] Henrik Zetterberg,[1,4] Blair R. Leavitt,[5] Rainer Kuhn,[2] Sarah J. Tabrizi,[1] Douglas Macdonald,[6] and Andreas Weiss[2]. (2015)

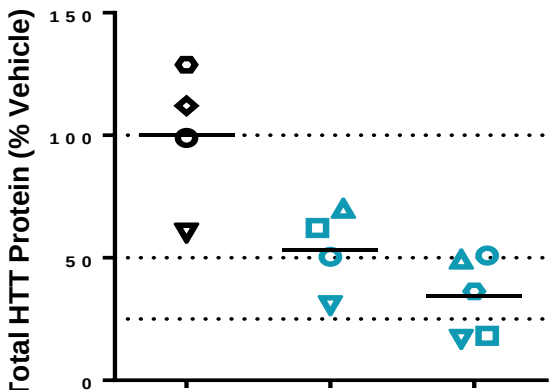


HTT Reduction in CSF Correlates with HTT Reduction in Cortex in Non-human Primates

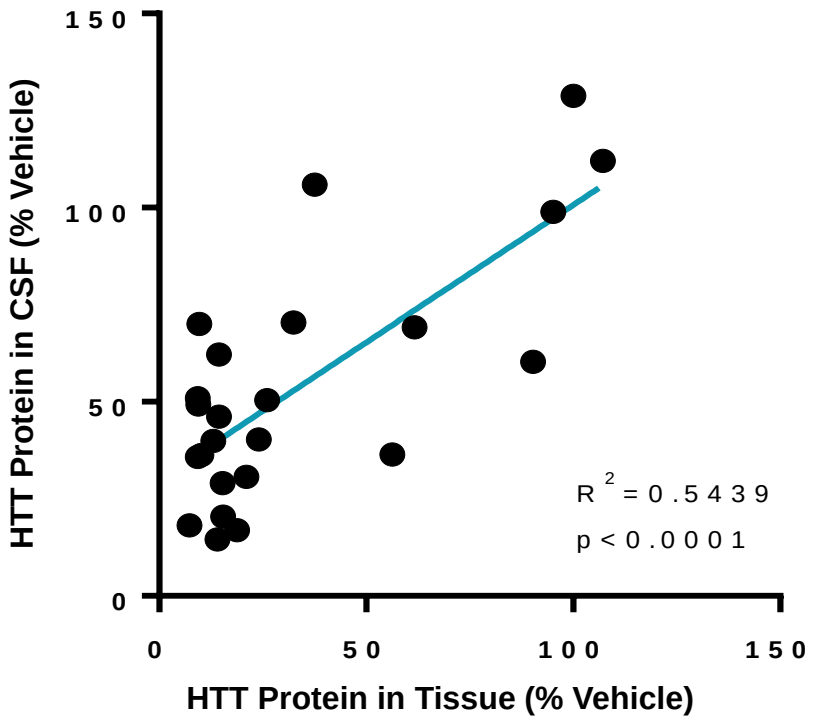
HTT Protein in Frontal Cortex



HTT Protein in CSF



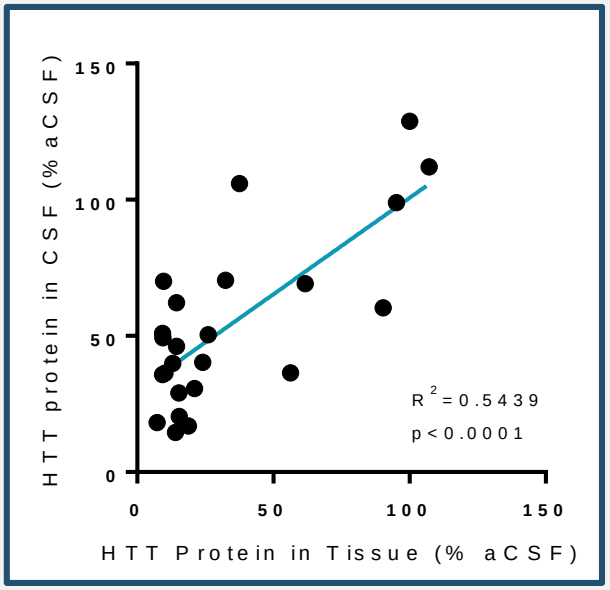
Correlation of HTT Reduction in CSF and Cortex

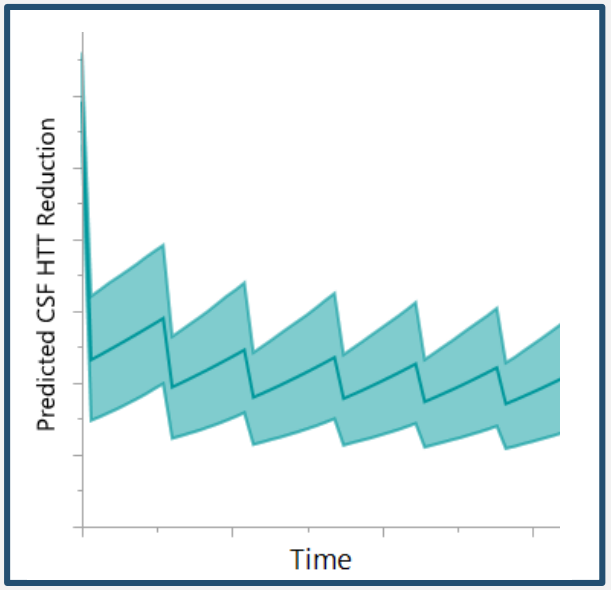


CSF = cerebrospinal fluid

Extensive Preclinical Studies Inform a PK/PD Model to Predict Human CSF and Tissue mHTT Lowering

- Built from data collected in rodents and NHPs
- Predicts effect of a given dose of antisense drug on human CSF mHTT levels
- Guides interpretation of observed antisense drug-mediated changes in human mHTT CSF level to tissue lowering prediction (e.g. reduction in cortex)





mHTT Protein Reduction Model Prediction		
CSF	Cortical Tissue (predicted)	Caudate Tissue (predicted)
40%	55-70%	20-35%
60%	70-85%	35-50%

PK = pharmacokinetic; PD = pharmacodynamic

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Comprehensive Preclinical Package Supports Clinical Program in HD Patients (1/2)

- **Can Generation 2+ antisense drugs target HTT in the brain?**
  - ✓ HTT-targeting antisense drugs distribute broadly in CNS and produce robust reductions of HTT mRNA and protein with IT administration
- **Are HTT-targeting drugs efficacious in disease models of HD?**
  - ✓ HTT-targeting antisense drugs produced durable reduction in huntingtin mRNA and protein in a mouse model of HD
  - ✓ HTT-targeting antisense drugs improved motor function and prolong survival in mouse models of HD
- **What is the optimal approach for targeting HTT?**
  - ✓ Total HTT-targeting antisense drugs demonstrate best approach with:
    - More robust activity compared to mutant only drugs
    - Good safety and tolerability
    - Potential to treat all HD patients with one drug

Comprehensive Preclinical Package Supports Clinical Program in HD Patients (2/2)

- **Are total HTT-targeting drugs safe in preclinical studies?**
  - ✓ Comprehensive preclinical package demonstrates that targeting total HTT is safe and well tolerated
- **Can mHTT be used to verify dose/target engagement?**
  - ✓ Sensitive and reproducible assay for mHTT in CSF
  - ✓ PK/PD model developed to predict mHTT reduction by dose in CSF and in brain regions, such as the cortex

Based on positive preclinical efficacy and safety data we and Roche decided to advance IONIS-HTT$_{Rx}$ into clinical studies

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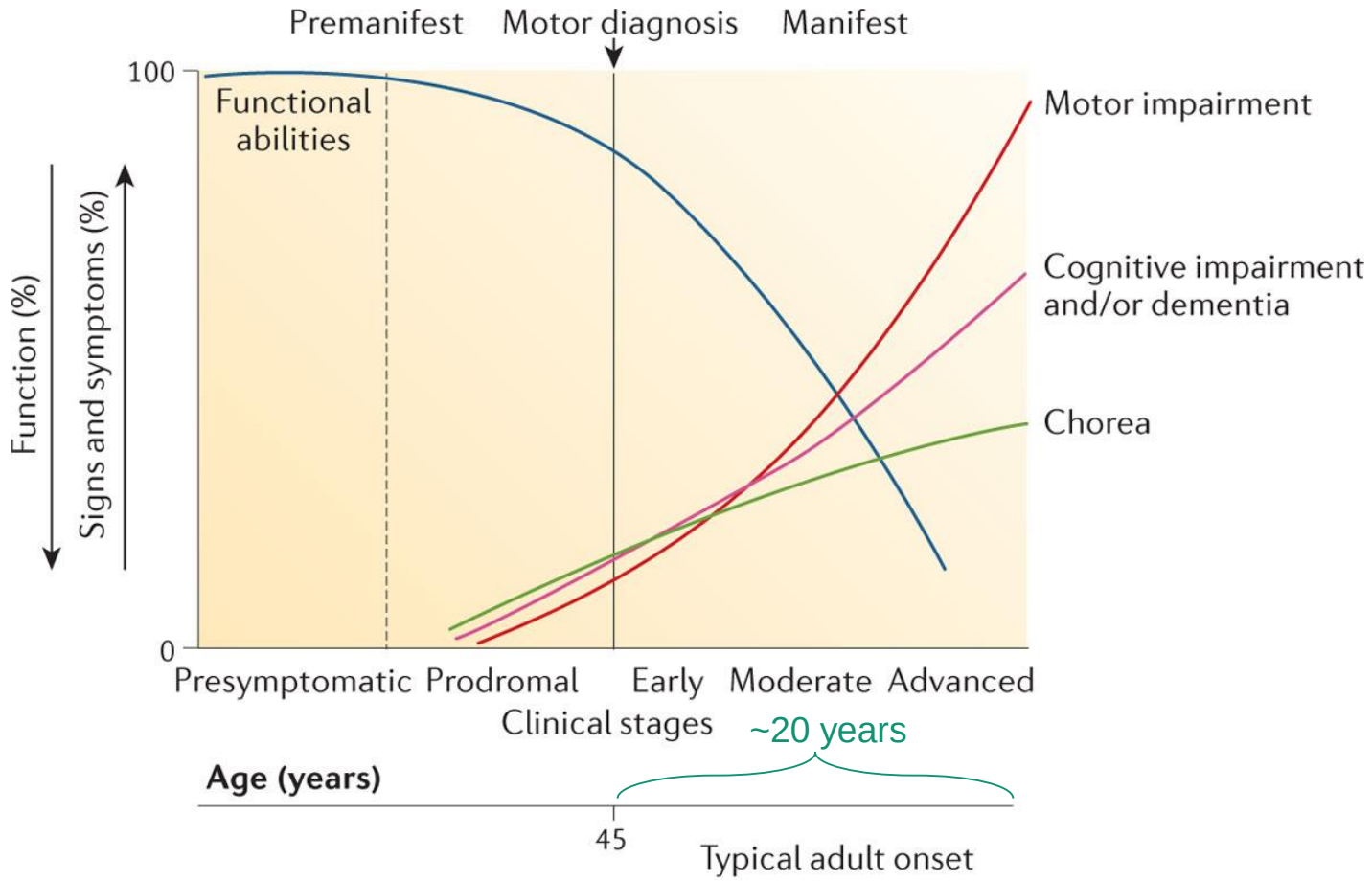
- **Conclusion and Q&A**	Stanley Crooke, M.D., Ph.D.

Natural History of Clinical HD is Well Understood



Tabrizi, S. J. et al. (2015) Huntington disease. Nat. Rev. Dis. Primers

Multi-center, Multi-national, Prospective, Observational Natural History Study

TRACK-HD aims to:

- Help understand neurobiology of pre-manifest and early HD
- Identify predictors of onset and modifiers of progression
- Establish clinical trial measures and methodology

Clinical Trial design: rigorous training, data monitoring, blinded QC/QA, centralized analysis

4 study sites:
London (UCL)
Leiden (LUMC)
Paris (UPMC)
Vancouver (UBC)

- 123 Controls
- 120 Premanifest: 62 PreA, 58 PreB
- 123 Early HD: 77 HD1, 46 HD2

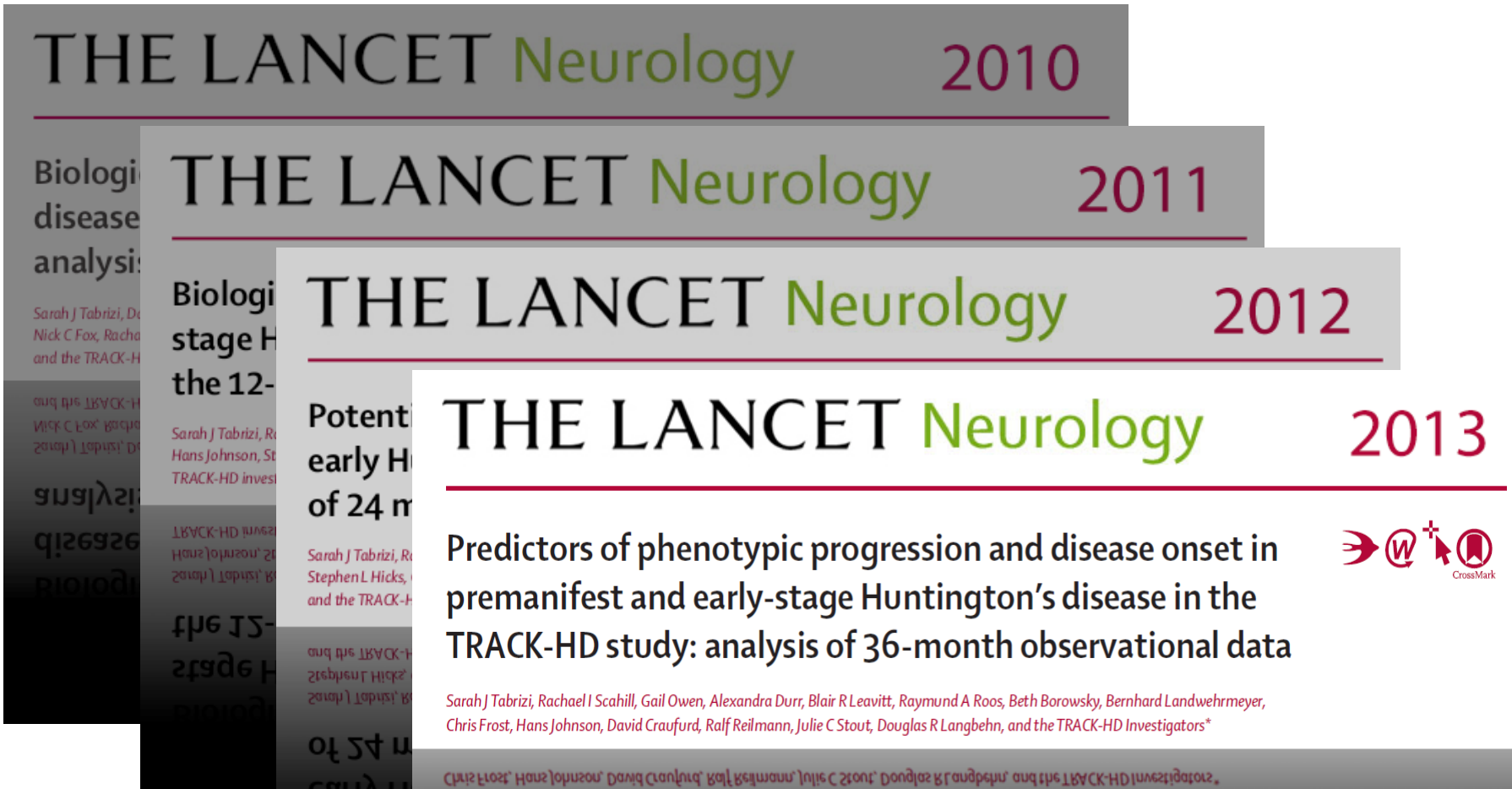
- 3T MRI (DTI, PET, MRS)
- Novel quantitative motor tasks
- Cognitive battery
- Oculomotor tasks
- Videotaped psychiatric assessment
- Blood biosamples
- Quality of life, and functional assessments

Baseline 2008
12-month 2009
24-month 2010
36-month 2011

Tabrizi et al., Lancet Neurology 2009, 2011, 2012, 2013

TRACK-HD

- Insights into Huntington's disease natural history pre- and post-symptom-onset
- TRACK-HD battery now used in current global clinical trials



Examples of the Best Performing Clinical Outcome Measures in HD

Unified Huntington's Disease Rating Scale (UHDRS)

- Assesses motor function, behavioral function, cognitive function and functional capacity. Three commonly-reported subdomains:
  - Total Functional Capacity (TFC): 0-13 point scale (higher number = higher function)
  - Total Motor Score (TMS): 0-124 point scale (higher number = greater impairment)
  - Independence Scale: 0-100 point scale (higher number = more independence)

Symbol Digit Modalities Test (SDMT)

- Test of attention, visuoperceptual processing, working memory and psychomotor speed (higher score = better functioning)

Stroop Word Reading Test (SWR)

- Test of processing and psychomotor speed (higher score = better functioning)

TRACK-HD Summary

- TRACK-HD showed clinically significant changes in brain imaging over one year in early stage HD
- Changes in cognition and motor testing had the largest effect sizes of all UHDRS and non-UHDRS measures studied, but were only significant over approximately two years in early HD patients

Based on TRACK-HD, a greater than one-year study with hundreds of patients is necessary to show potential benefit in clinical outcomes

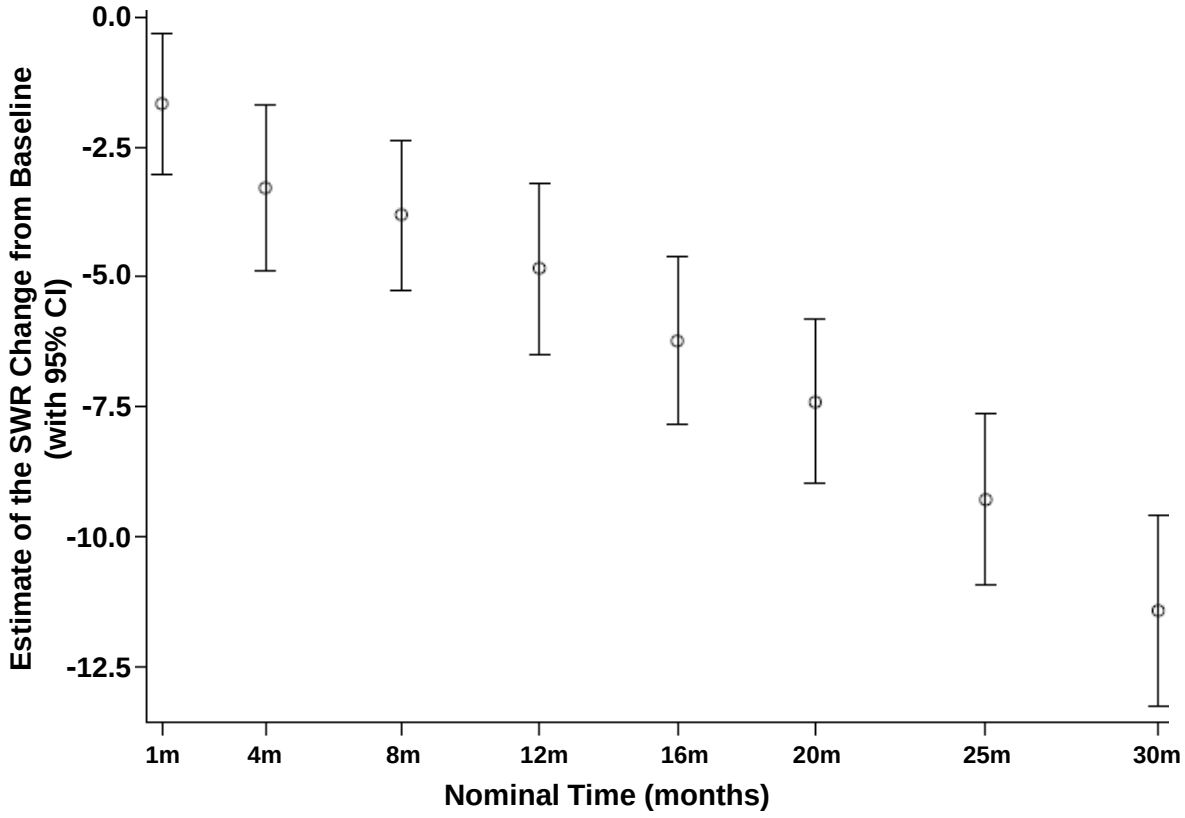
Benefit in Clinical Outcomes Likely to Require >1-year Study and Hundreds of Patients

Example: Stroop Word Reading Test

- 30-month outcome data in placebo group from early HD (TFC 7-13) from CARE-HD study
- Change from baseline increases as a linear function of time
- >1 year needed to see significant change from baseline

Stroop Word Reading

Longitudinal change in early stage HD over 30 months (n=173)

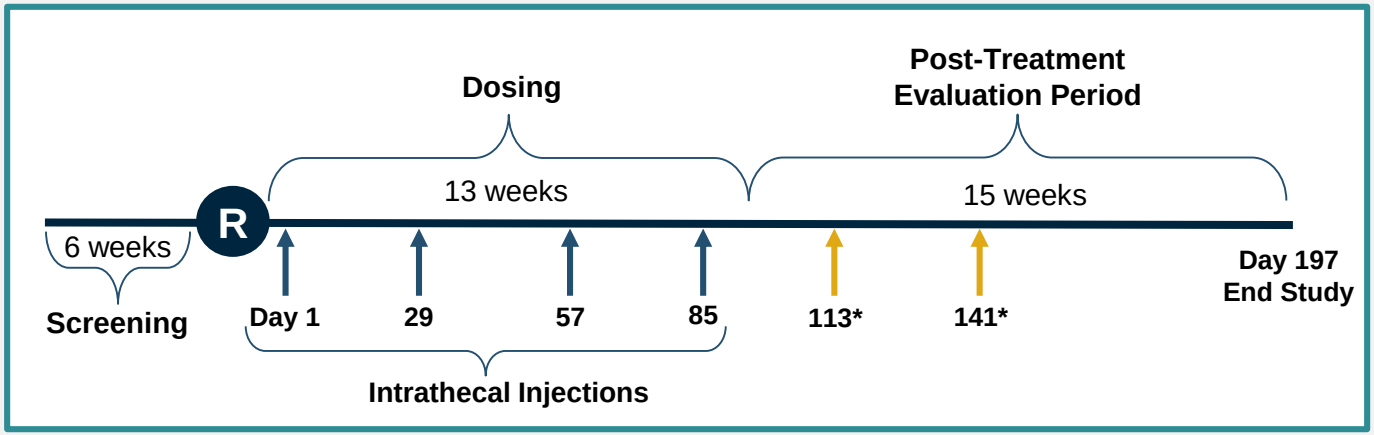


IONIS-HTT$_{Rx}$ (RG6042) Phase 1/2 Study

IONIS-HTT$_{Rx}$ (RG6042) Phase 1/2 Study Design

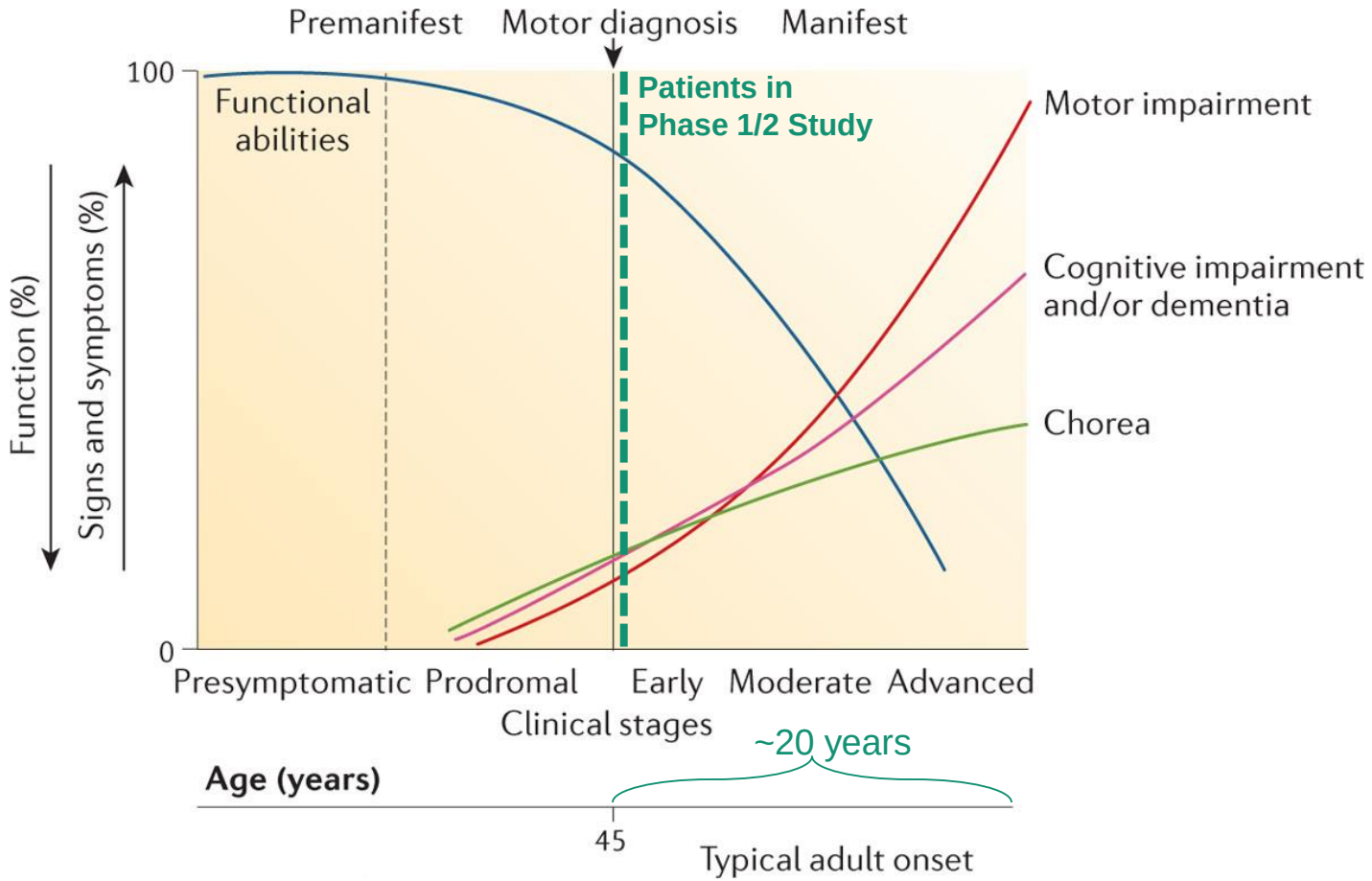
- A randomized, double-blind, placebo-controlled, multiple ascending dose study in 46 adult patients with early stage Huntington's disease
- Primary Objective:
  - Evaluate the safety and tolerability of ascending doses of multiple intrathecal administrations of IONIS-HTT$_{Rx}$
- Secondary Objective:
  - Evaluate pharmacokinetic (PK) profile of IONIS-HTT$_{Rx}$ in cerebrospinal fluid (CSF)
- Exploratory Objective:
  - Evaluate effect of IONIS-HTT$_{Rx}$ on CSF mHTT protein
- Conducted at 9 sites worldwide (UK, Germany, Canada)

Cohorts	IONIS-HTT$_{Rx}$ (n)	PBO (n)
10 mg	3	1
30 mg	6	2
60 mg	6	2
90 mg	9	3
120 mg	10	4



*Half of patients received lumbar puncture at Day 113 and half at Day 141 to sample; ↑ = IT dose; ↑ = sample

Natural History of Clinical HD



Tabrizi, S. J. et al. (2015) Huntington disease. Nat. Rev. Dis. Primers

IONIS-HTT$_{Rx}$ (RG6042) Phase 1/2: Early Stage HD Patient Population

Baseline Characteristics

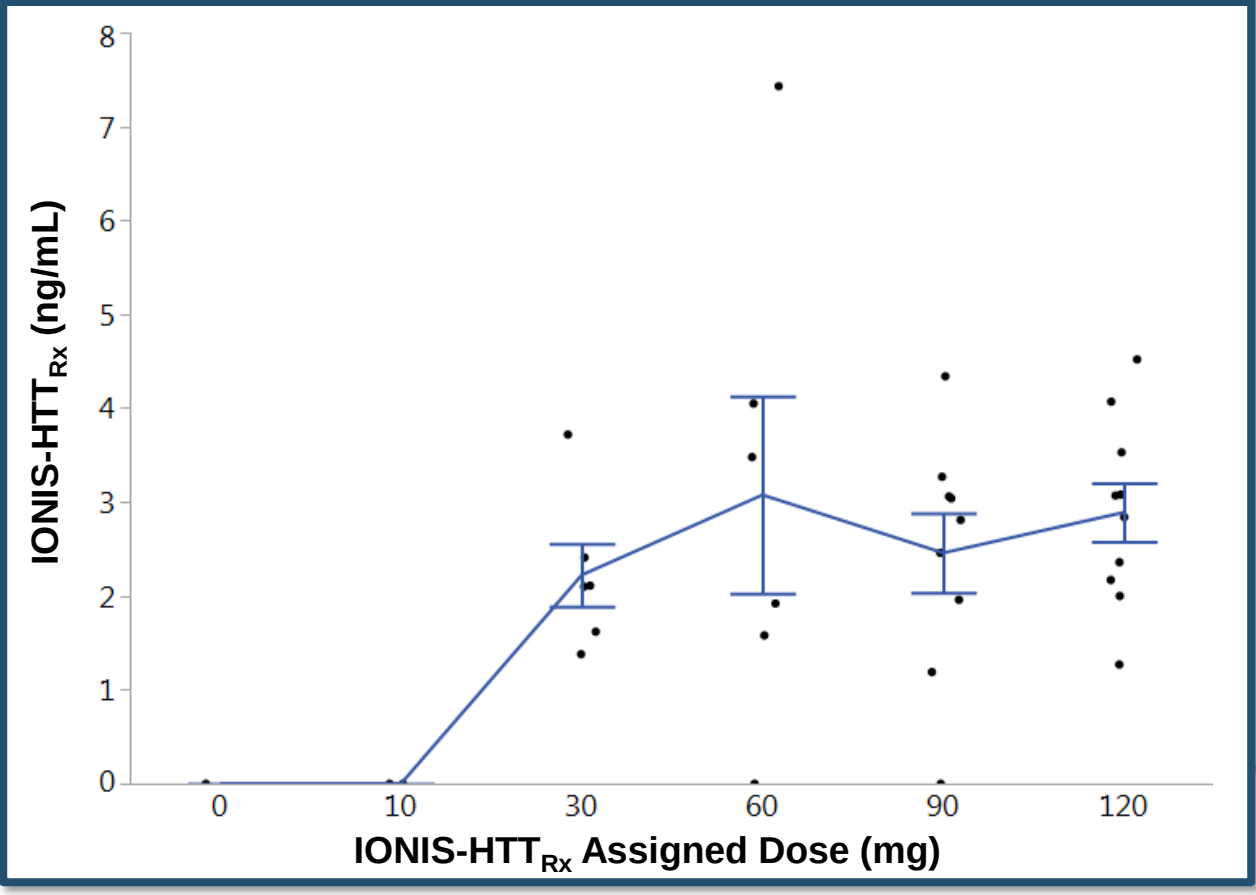
	IONIS-HTT$_{Rx}$ (N=34)	Placebo (N=12)
Age (yr)		
Mean (SD)	46 (10)	49 (10)
Range	26 – 65	31 – 65
Gender		
Male – N (%)	20 (59%)	8 (67%)
Female – N (%)	14 (41%)	4 (33%)
TFC		
11 – N (%)	9 (26%)	6 (50%)
12 – N (%)	15 (44%)	4 (33%)
13 – N (%)	10 (29%)	2 (17%)
CAG repeats		
Mean (SD)	44 (3)	44 (2)
Range	40 – 55	41 – 50
mHTT at Baseline (fM)		
Mean (SD)	110 (46)	109 (43)
Range	31 - 203	53 – 185

TFC = Total Functional Capacity

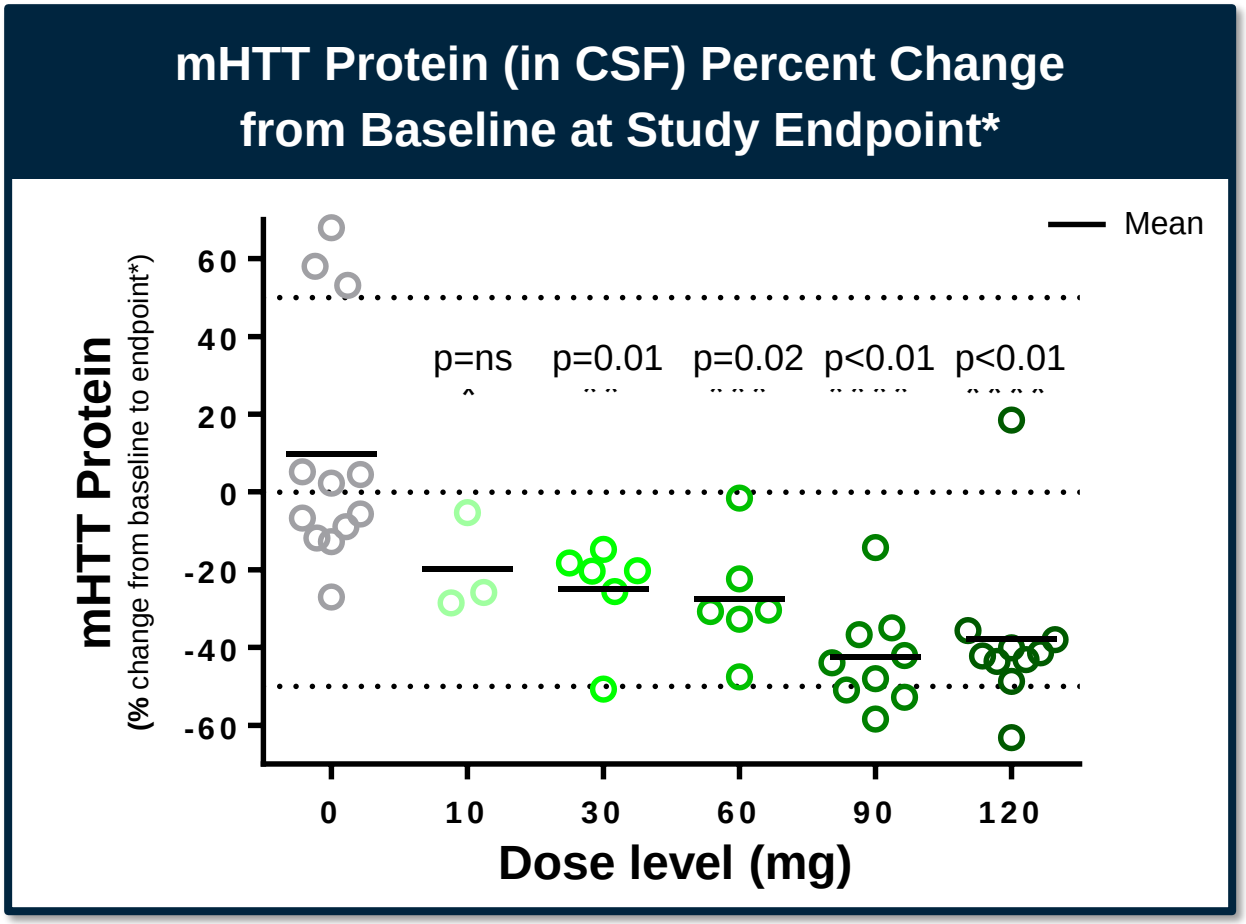
Potential Drug Saturation of CNS Tissue

IONIS-HTT$_{Rx}$ in CSF

(Maximum value in each patient 1 month after dosing)



Treatment with IONIS-HTT$_{Rx}$ (RG6042) Demonstrates Dose-dependent Reduction in CSF mHTT

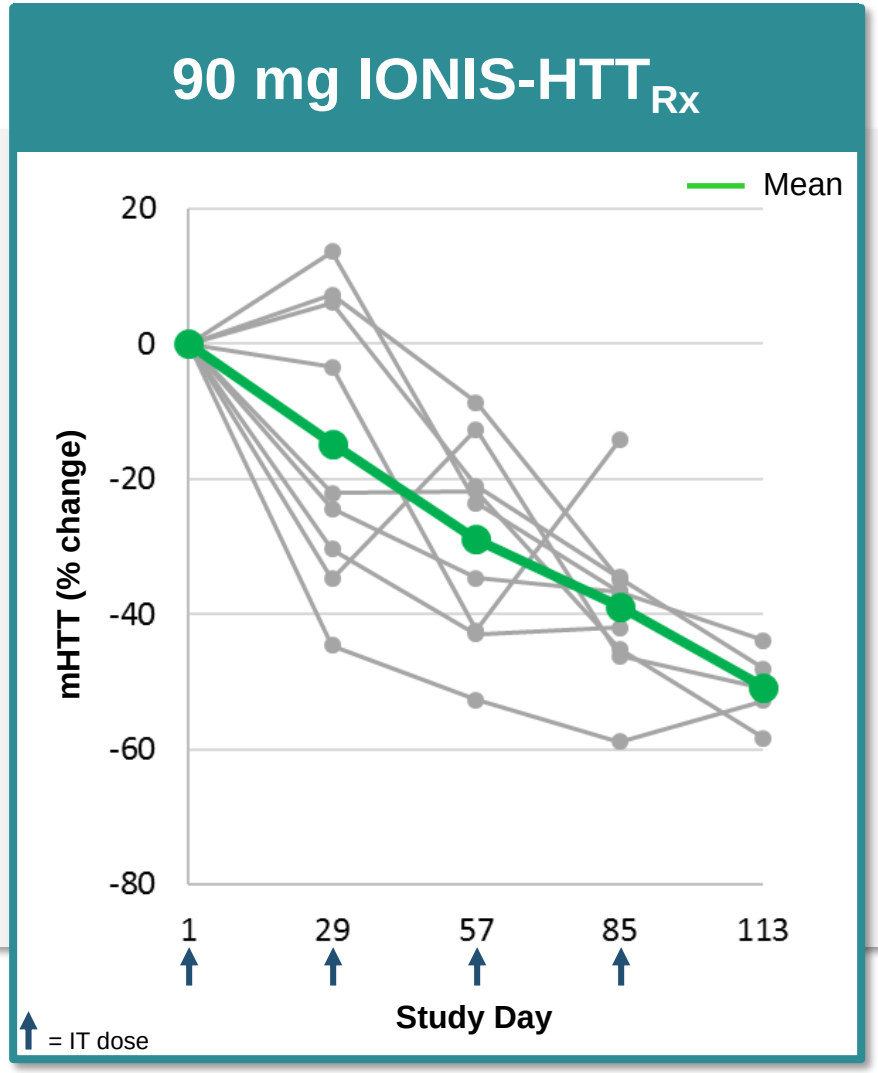


The magnitude of mHTT reduction in CSF exceeds the reductions that produced disease modification in animal models of HD

*Endpoint is defined as the later of Day 85 and 113

Further Decrease in mHTT Anticipated with Maximum Reduction Expected in Approximately Six Months

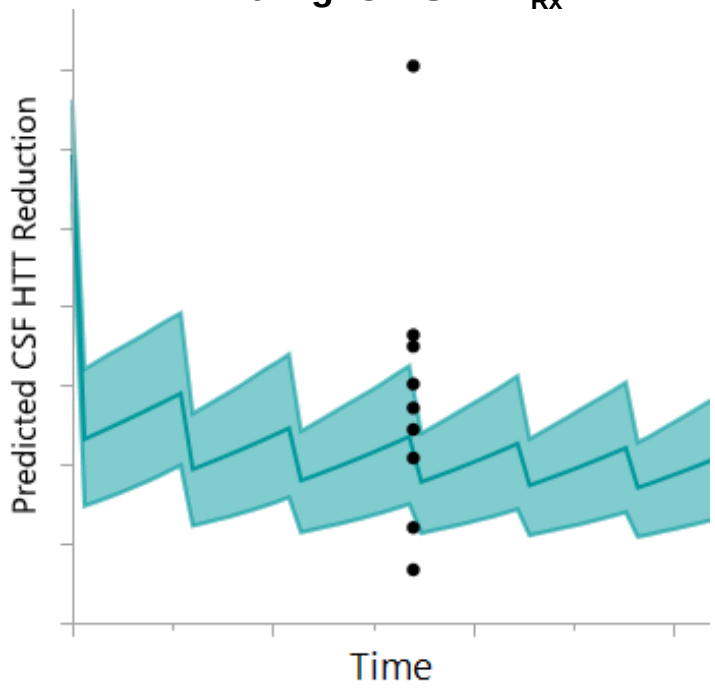
- mHTT levels still declining at three months of treatment with IONIS-HTT$_{Rx}$
  - In ~70% (23/34) of patients assigned to IONIS-HTT$_{Rx}$ (RG6042), mHTT is declining at last trough measurement



Preclinical PK/PD Model is Highly Predictive of the Clinical Data

Study Planning → **Study Conclusion**

120 mg IONIS-HTT$_{Rx}$



Clinical data fit well with predicted model

mHTT Protein Reduction		
CSF (measured)	**Cortical Tissue** (predicted)	**Caudate Tissue** (predicted)
40%	55-70%	20-35%
60%	70-85%	35-50%

mHTT reductions of 40-60% in CSF correspond to an estimated 55-85% reduction in the cortex

IONIS-HTT$_{Rx}$ (RG6042) was Safe and Well Tolerated

- No participants discontinued from the study throughout 7-month treatment and follow-up period
- Most adverse events (AEs) were mild and considered to be unrelated to study drug
- No severe AEs
- Post-lumbar puncture (LP) headaches after ~10% of LPs; no blood patches
- No clinically-meaningful changes in safety laboratory parameters
- No serious AEs in patients treated with IONIS-HTT$_{Rx}$
- One serious AE in a placebo-treated patient:
  - Mild post-LP headache
  - Hospitalization for observation
  - Resolved without sequelae

Adverse Event Profile Supports Further Development

Events observed in greater than 5 patients who received IONIS-HTT$_{Rx}$

System Organ Class Preferred Term	Placebo (N=12)		IONIS-HTT$_{Rx}$-treated (N=34)	
	Patients (%)	Events	Patients (%)	Events
Patients reporting at least one adverse event	12 (100.0)	78	33 (97.1)	216
Injury, poisoning and procedural complications				
Procedural pain	6 (50.0)	12	19 (55.9)	45
Post lumbar puncture syndrome	5 (41.7)	11	12 (35.3)	24
Fall	3 (25.0)	5	7 (20.6)	8
Infections and infestations				
Nasopharyngitis	2 (16.7)	3	7 (20.6)	7
Nervous system disorders				
Headache	6 (50.0)	13	6 (17.6)	15

IONIS-HTT$_{Rx}$ (RG6042): The First Successful HTT-lowering Drug

IONIS-HTT$_{Rx}$ demonstrated robust and dose-dependent lowering of mHTT, the underlying cause of HD, in early stage patients

- Average reduction of approximately 40-60% in mHTT in CSF at two high-dose regimens, corresponds to 55-85% reduction of mHTT in brain cortex and 20-50% in caudate
- Data suggest continued dosing with IONIS-HTT$_{Rx}$ will result in further reduction
- The magnitude of mHTT reduction in CSF exceeds the reductions that produced disease modification in animal models of HD

IONIS-HTT$_{Rx}$ was safe and well tolerated at all doses tested in Phase 1/2 study

Roche and Ionis are working to quickly advance IONIS-HTT$_{Rx}$ to a pivotal efficacy study

Open-label study ongoing for patients who participated in the Phase 1/2 study

We will continue to evaluate IONIS-HTT$_{Rx}$ and report additional results at future medical conferences

Thank You to All Participants and Colleagues

Huntington's Patients and Their Families

Hugh Rickards
University Hospitals Birmingham, UK

Bernhard Landwehrmeyer
Ulm University, Germany

Roger Barker
Cambridge University, UK

Blair Leavitt
University of British Columbia, Canada

Sarah Tabrizi
University College London, UK

David Craufurd
University of Manchester, UK

Anne Rosser
University Hospital of Wales, UK

Carsten Saft
Ruhr-University Bochum, Germany

Josef Priller
Charité University Berlin, Germany

All Principal Investigators and their staff

IONIS PHARMACEUTICALS

Roche

CHDI FOUNDATION

Webcast Agenda

Topic	Speaker
- **Welcome and Introductions**	Stanley Crooke, M.D., Ph.D.
- **Huntington's Disease Background** - **Preclinical Data**	Frank Bennett, Ph.D.
- **Phase 1/2 Clinical Data**	Sarah Tabrizi, M.D., Ph.D., FMedSci
- **Goals of Clinical Efficacy Testing** - **Next Steps**	Scott Schobel, M.D., M.Sc., Roche
- **Conclusion and Q&A**	Stanley Crooke, M.D., Ph.D.

Towards a Brighter Future for Patients with HD

Building on strong science and partnerships

Apr 2013

Ionis / Roche partnership

Sep 2015

First patient in Phase 1/2 study in HD

2015 - 2017

TAE adboards, first site visits

mHTT assay Clinical and Digital EP development

Nov 2017

Phase 1/2 data readout

Dec 2017

Roche licenses IONIS-HTT$_{Rx}$

EP = endpoint

Roche's Vision for IONIS-HTT$_{Rx}$ (RG6042) for Patients with HD

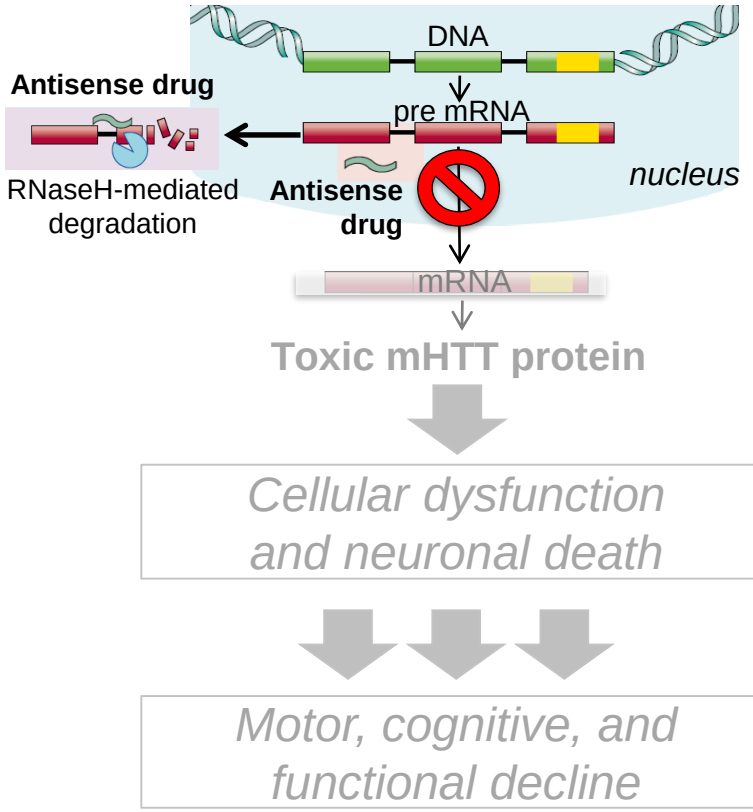
HD: No therapy available to stop disease onset and clinical progression

HD (*HTT* gene CAG repeats >35) → toxic mHTT protein

After a long period of being at risk, 50% of offspring of parent with HD gene experience onset of motor, cognitive, behavioral, and functional decline

IONIS-HTT$_{Rx}$ (RG6042): Target the cause, change clinical outcomes

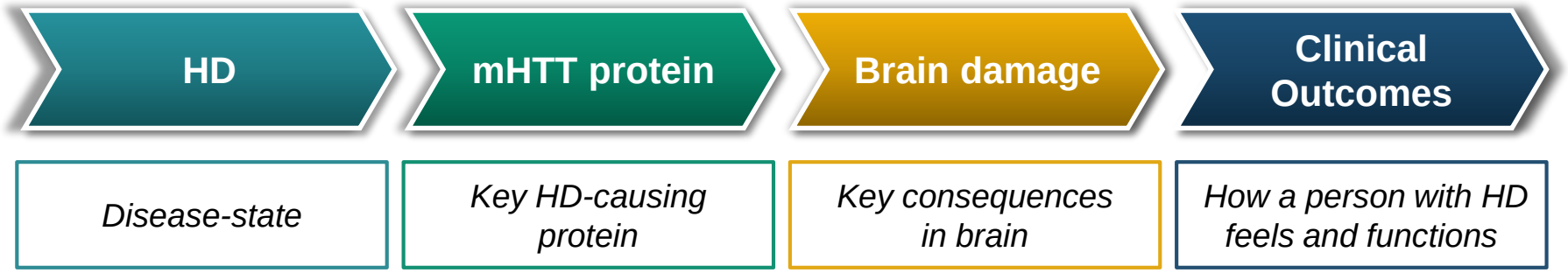
Upstream targeting of HTT with HTT-targeting antisense drugs



MOA schema adapted from Tabrizi and Wild, Lancet Neurology, 2017

Immediate Goal: Demonstrate that HTT Lowering Improves Huntington's Disease

Key idea of how mutant protein impacts brain, body, and behavior



Immediate program goals:

- Investigate how lowering of the mHTT protein affects the brain, body, and how a person with HD feels and functions
  - Investigate objective markers of drug effect in open-label extension study
  - Investigate further longitudinal causal pathway in natural history studies (e.g. UCL HD-CSF)
- Generate longer-term safety and tolerability information of the antisense drug injected through IT route

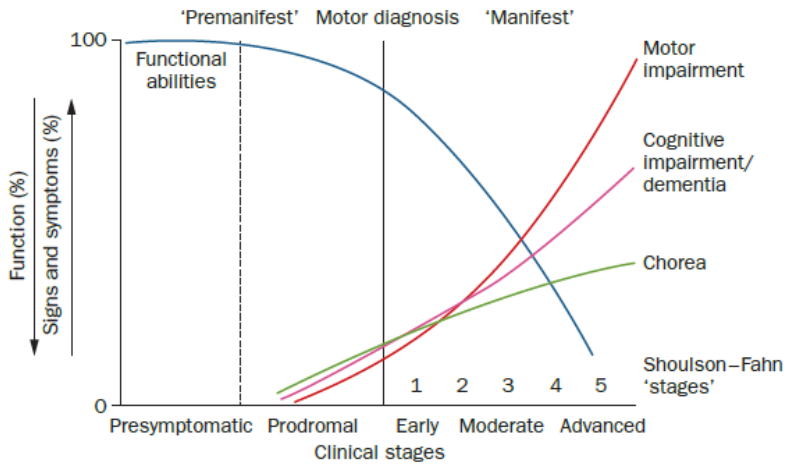
Publication Showing Motor, Cognitive, and Functional Declines Contribute to a Single Progressive Factor in Early HD

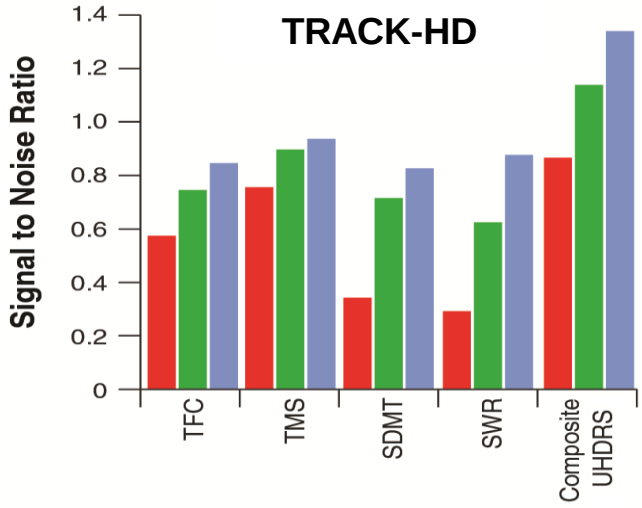
AMERICAN ACADEMY OF NEUROLOGY®

The most widely read and highly cited peer-reviewed neurology journal

Motor, cognitive, and functional declines contribute to a single progressive factor in early HD

Schobel SA, Palermo G, Auinger P, Long JD, Ma S, Khwaja OS, Trundell D, Cudkowicz M, Hersch S, Sampaio C, Dorsey ER, Leavitt BR, Kieburtz KD, Sevigny JJ, Langbehn DR, Tabrizi SJ; TRACK-HD, COHORT, CARE-HD, and 2CARE Huntington Study Group Investigators.





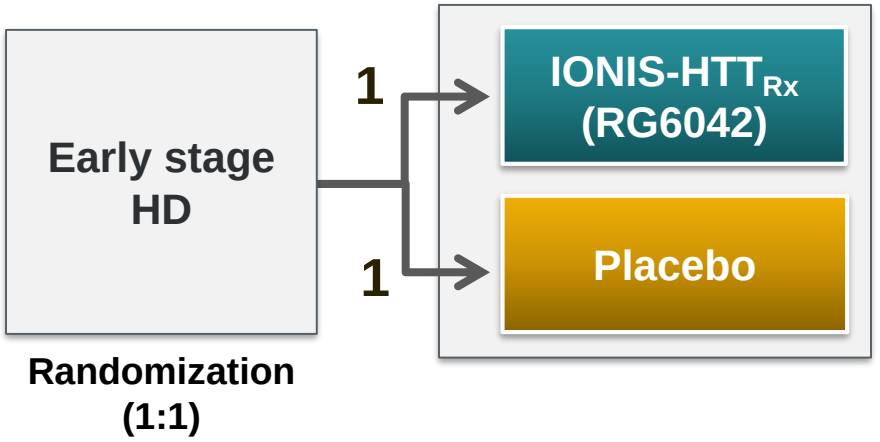
- **Motor, cognitive, and linked functional decline have a reliable pattern of progression** and when used together significantly enhance measurement sensitivity—the 'composite UHDRS' (Schobel 2017)
- Other **behavioral domains are fundamentally episodic**

The Payoff: More Efficient Clinical Trials with a More Holistic Outcome

Sample size required for two-arm trial

Duration (Year)	Treatment Effect	Measure				
		cUHDRS	TMS	TFC	SDMT	SWR
2	25%	430	960	1096	984	1059
2	50%	108	240	274	246	265
2	75%	48	107	122	109	118
3	25%	341	634	858	590	539
3	50%	85	158	215	148	135
3	75%	38	70	95	66	60

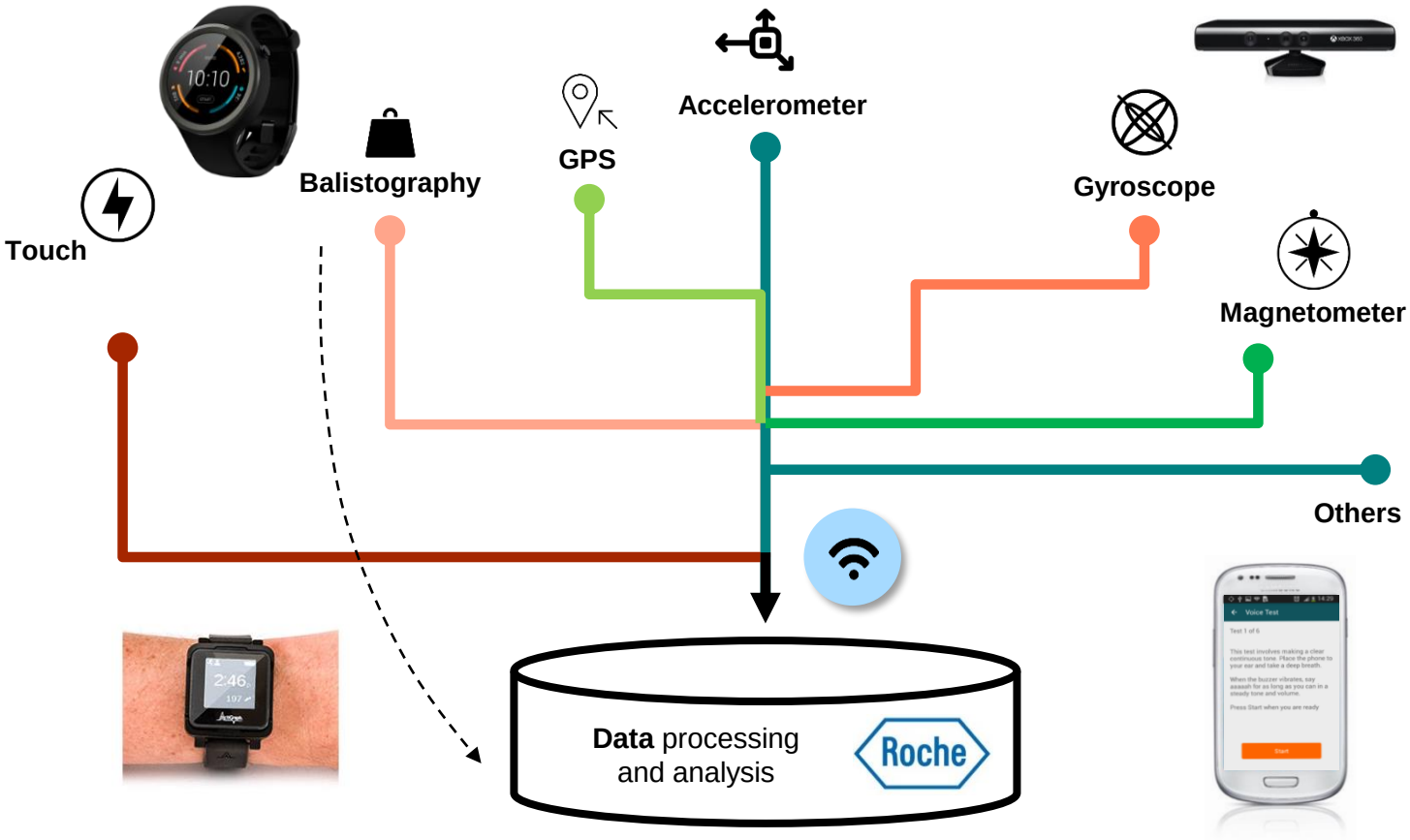
Illustrative design depicted



Conclusion:

- Use of the cUHDRS provides gains to study efficiency, helping accelerate delivery of promising drugs to patients

Extending Measures of Clinical Progression into the Real World



PRO's	In-Clinic Active Tests	Active Tests	Passive Monitoring
Surveys	All Active Tests; Gait (&25FW); Balance; Turn/TUG	Cognition & Dysarthria; Dexterity & Bradykinesia; Chorea; Lower Body Bradykinesia	Gait; Chorea; Activity levels
Daily Question; EQ5D5L			

Assessments anchored to UHDRS items

Next Steps: Roche Advancing IONIS-HTT$_{Rx}$ (RG6042)Toward the Market

- Open-label extension study is underway and rapidly enrolling
- Investigate causal pathway further and how mHTT lowering is linked to clinical outcomes in people with HD
- Develop clinical endpoint strategy to measure effects of IONIS-HTT$_{Rx}$ (RG6042) on clinical progression with maximal sensitivity
- Initiate a pivotal clinical efficacy study, including U.S. sites

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IONIS-HTT$_{Rx}$ (RG6042): First and Only Drug to Demonstrate Robust, Dose-dependent Reductions of mHTT in HD Patients

Up to ~60% (~40% mean) reduction of mHTT in CSF after three months of treatment, with reductions continuing

We expect the planned dosing regimen for IONIS-HTT$_{Rx}$ to result in optimal target reduction

HD is a significant area of unmet need with 30,000 patients diagnosed in the U.S. and 200,000 at-risk

Initial data supports the potential of IONIS-HTT$_{Rx}$ to safely treat all patients with Huntington's Disease (HD)

Roche and Ionis are working to quickly advance IONIS-HTT$_{Rx}$ to a pivotal clinical efficacy study

Ionis is Continuing to Advance Industry-leading Neurological Disease Franchise

1 **Highly Successful CNS Drug on the Market**

SPINRAZA – *"One of the most successful rare disease drug launches in history"*

1 **Drug Under Regulatory Review**

Inotersen – "*Potential to transform the lives of patients with hATTR"*

4 **Drugs in Development**

- IONIS-HTT$_{Rx}$ (RG6042)
- IONIS-SOD1$_{Rx}$
- IONIS-MAPT$_{Rx}$
- ATL1102

6 **Drugs in Preclinical**

- IONIS-TTR-L$_{Rx}$
- IONIS-C9$_{Rx}$
- IONIS-BIIB6$_{Rx}$
- IONIS-BIIB7$_{Rx}$
- IONIS-BIIB8$_{Rx}$
- IONIS-DNM2-2.5$_{Rx}$

More than 20 wholly owned and partnered drug discovery programs

For Alzheimer's, Parkinson's, ALS, pain and multiple rare neuro diseases

Key Upcoming Milestones in 2018

5 **Drugs Potentially On the Market**

- SPINRAZA
- KYNAMRO
- Inotersen
- Volanesorsen
- Plazomicin

6 **Phase 2 Readouts**

- AKCEA-APO(a)-L_{Rx}
- AKCEA-ANGPTL3-L_{Rx}
- IONIS-$DGAT2_{Rx}$
- IONIS-HTT_{Rx} (RG6042)
- IONIS-$SOD1_{Rx}$
- IONIS-PKK_{Rx}

6 **Phase 2 or 3 Initiations**

- IONIS-$STAT3\text{-}2.5_{Rx}$
- IONIS-HTT_{Rx} (RG6042)
- IONIS-$GHR\text{-}L_{Rx}$
- IONIS-$FB\text{-}L_{Rx}$
- IONIS-$AR\text{-}2.5_{Rx}$
- IONIS-$KRAS\text{-}2.5_{Rx}$

Multiple POC Initial Clinical Trial Readouts

Revolutionizing Medicine. Saving Lives.

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