



International Parkinson and
Movement Disorder Society
European Section



5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 12

EAN/MDS-ES: Hyperkinetic movement disorders (Level 2)

What's new in chorea?

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What's new in chorea?

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Disclosures

Consultancy / research funding
from Hoffman La Roche, Triplet
Therapeutics, Mitoconix, Takeda

Brief, abrupt, irregular,
unpredictable,
non-stereotyped
movements.



Fidgetiness
Semi-purposeful
Chorea
Athetosis
Ballismus





Hereditary or acquired?

Acquired causes of chorea

- If you think it's acquired, it probably is
- You will probably find a cause
 - Unilateral = stroke or SOL (including HIV)
 - Drugs
 - Inflammation
 - SLE, Sydenham's, PANDAs
 - Chorea gravidarum
 - Thyrotoxicosis
 - Polycythaemia rubra vera (*JAK2* V617F)
- ~~Senile chorea~~

- Neuroleptics
- Levodopa
- Antiepileptics
 - phenytoin
 - carbamazepine
 - valproate
 - gabapentin
- Central nervous system stimulants
 - amphetamines
 - cocaine
 - methylphenidate
- Benzodiazepines
- Oestrogen-containing oral contraceptives
- Lithium
- Dopamine agonists

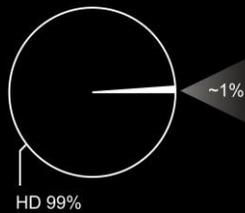
Wild & Tabrizi Practical Neurology 2007



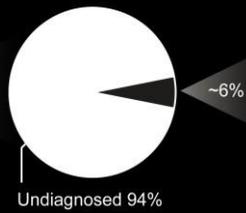
HD Phenocopies

- SCA1-3, NBIA, Benign hereditary chorea

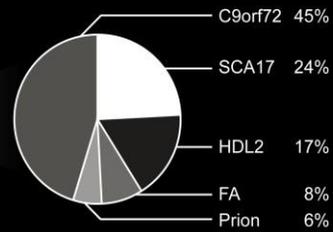
(a) Suspected HD cases



(b) HD phenocopy cases



(c) Genetically diagnosed phenocopies



Wild et al, Mov Disord 2007;
Wild et al, Curr Opin Neurol 2007;
Hensman Moss et al Neurology 2014

SCA17 ("HDL4" - *TBP*)

- Gait ataxia



Neuro-acanthocytosis



- Chorea-acanthocytosis due to *CHAC* mutations - chorein
- Oral dyskinesia
- Head-drop
- Macleod (XK) similar + organomegaly and neuropathy

Familial prion disease (*PRNP*)



C9orf72

- UMN signs

HDL2 (JPH3)





Research Article

Comparison of the Huntington's Disease like 2 and Huntington's Disease Clinical Phenotypes

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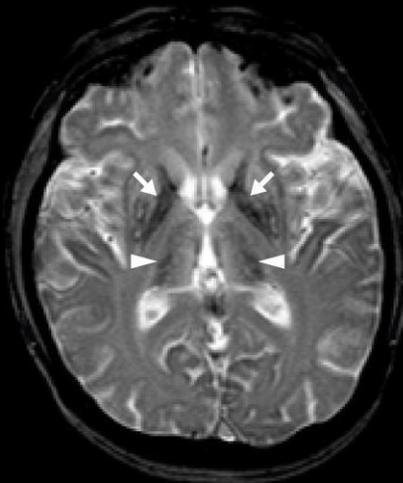
First published: 20 February 2019 | <https://doi.org/10.1002/mdc3.12742> | Cited by: 1

Conclusions

The HDL2 phenotype is similar to HD and is initially characterized by dementia, chorea, and oculomotor abnormalities, progressing to a rigid and bradykinetic state, suggesting the UHDRS is useful to monitor disease progression in HDL2. Although HDL2 patients scored higher on some UHDRS domains, this did not differentiate between the two diseases; it may however be emerging evidence of HDL2 having a more severe clinical phenotype.

- Not clinically different
- Probably no acanthocytes either

Neuroferritinopathy NBIA2 - *FTL* 1, ferritin light chain



Huntington's disease

Gait

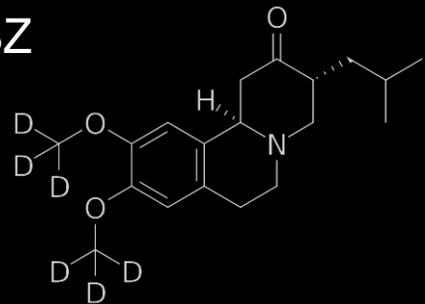


Treatment of chorea

1. Treat the **disability**, not the movement disorder
2. Could **neurophysiotherapy** be more helpful?
 - tinyurl.com/hdphysio
3. Treat **anxiety** to reduce chorea or its impact
4. Treat **mood** before giving **tetrabenazine**
5. Neuroleptics
 - Olanzapine
 - Sulpiride
 - Risperidone
 - Quetiapine

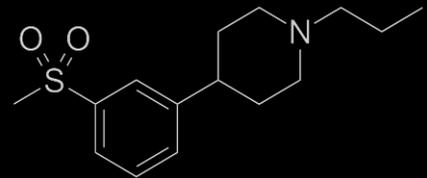
Deutetetrabenazine

- It works
- 2x instead of 3x daily
- Claims of improved side effect profile
- No direct comparison with TBZ
- Indirect comparisons show no difference

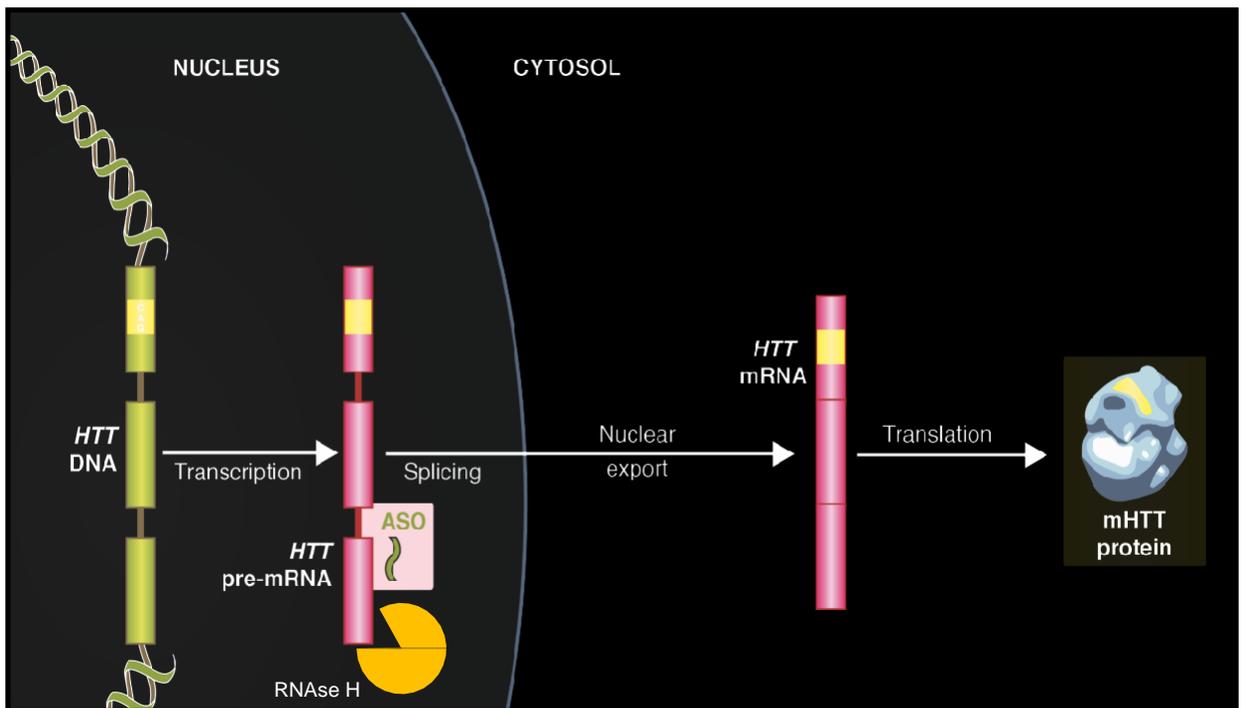
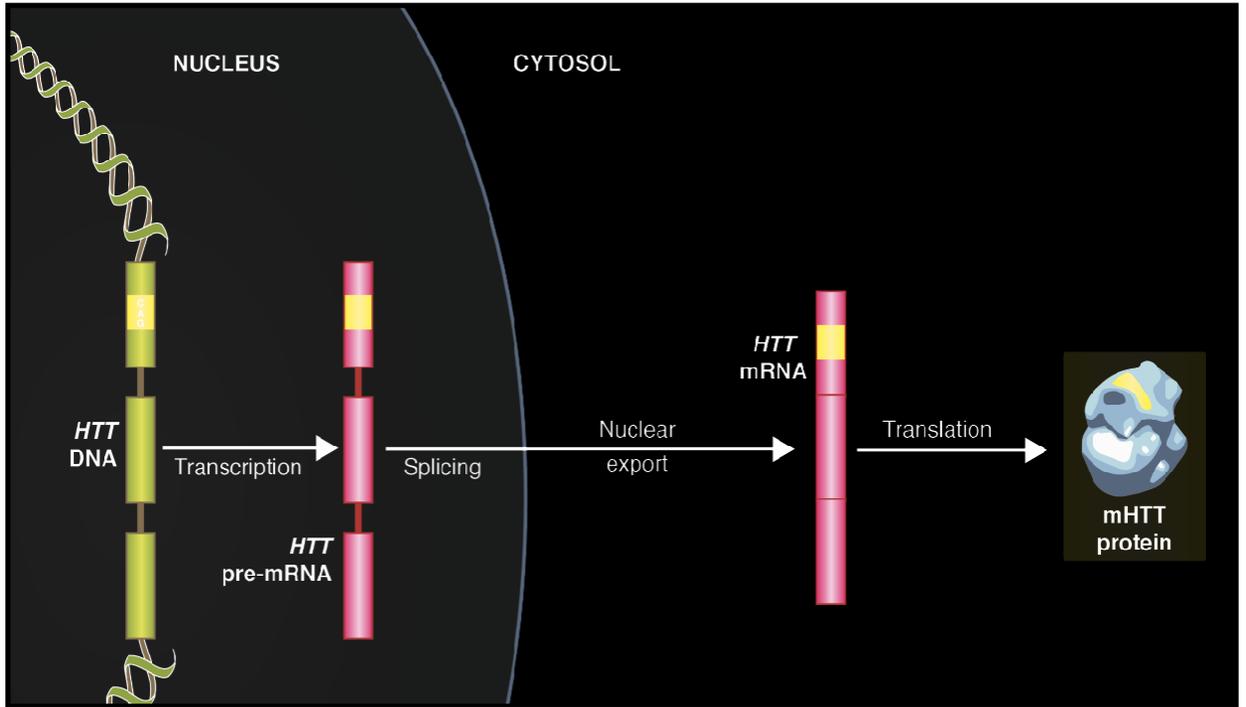


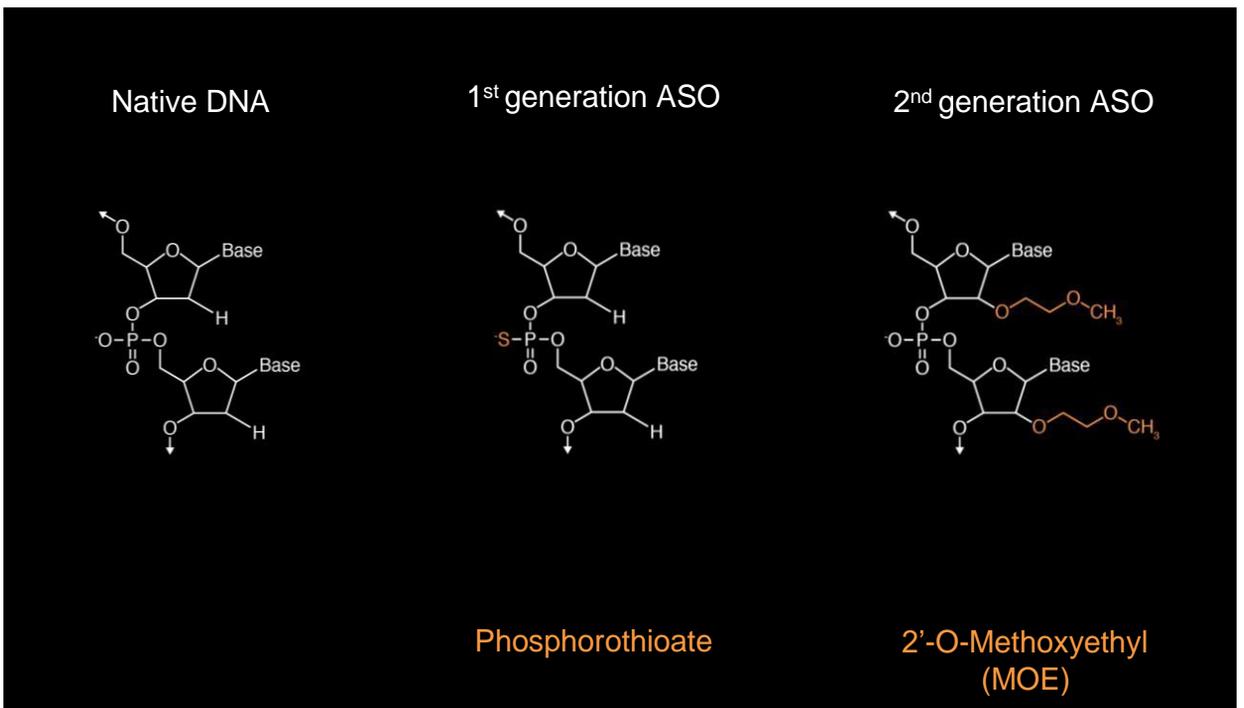
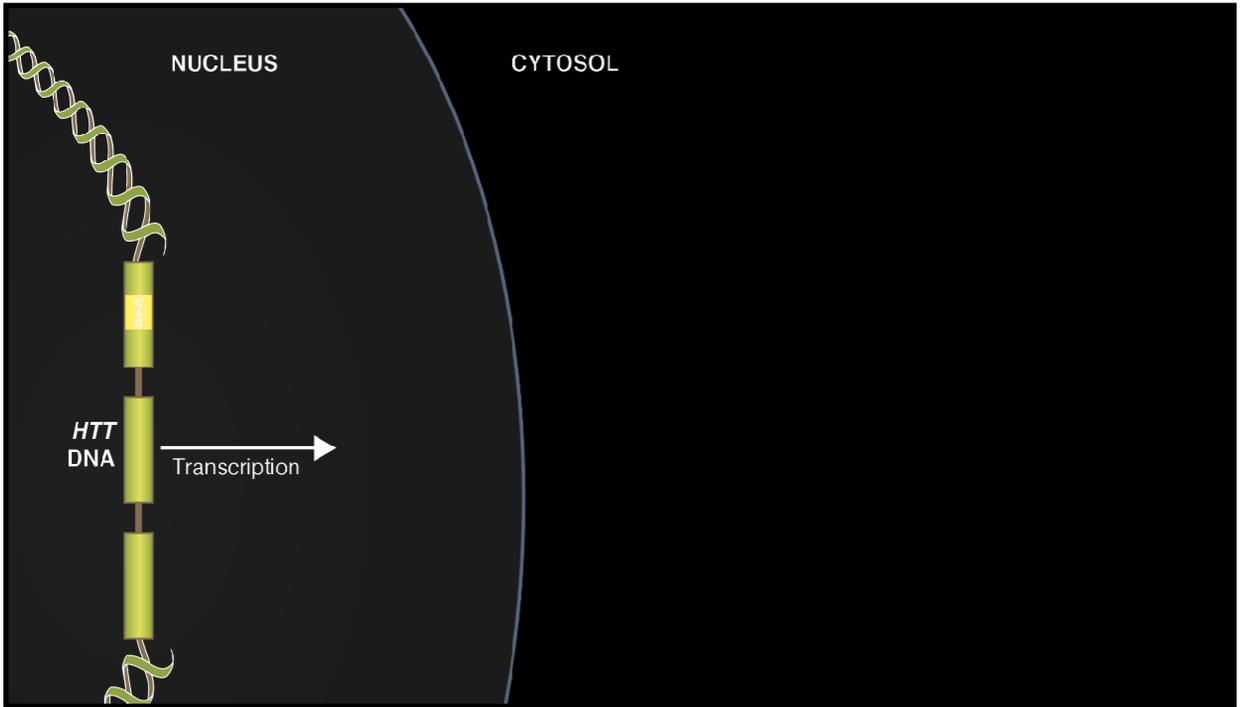
Pridopidine

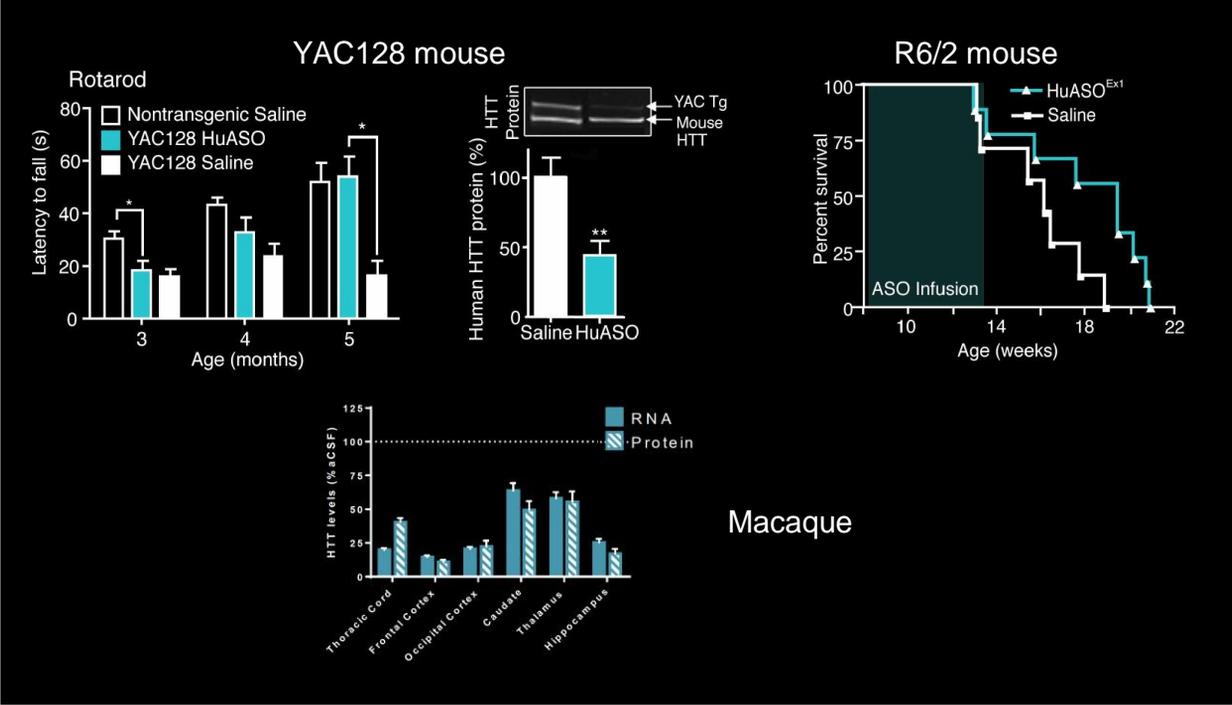
- “Dopaminergic stabilizer”
- Reduce chorea? Improve voluntary motor?
- Missed endpoints in 2× Ph2 and 1×Ph3 trial (PRIDE-HD)
 - Reilmann et al Lancet Neurology 2019
 - HDBuzz.net/227
- Now claimed to be disease-modifying sigma-1 agonist



Huntingtin lowering with RG6042,
an antisense oligonucleotide







First-in-Human Multiple Ascending Dose Study

Five dose levels vs placebo; 3:1 active to placebo; intrathecal bolus injection

Primary objective

Safety and tolerability

Secondary objective

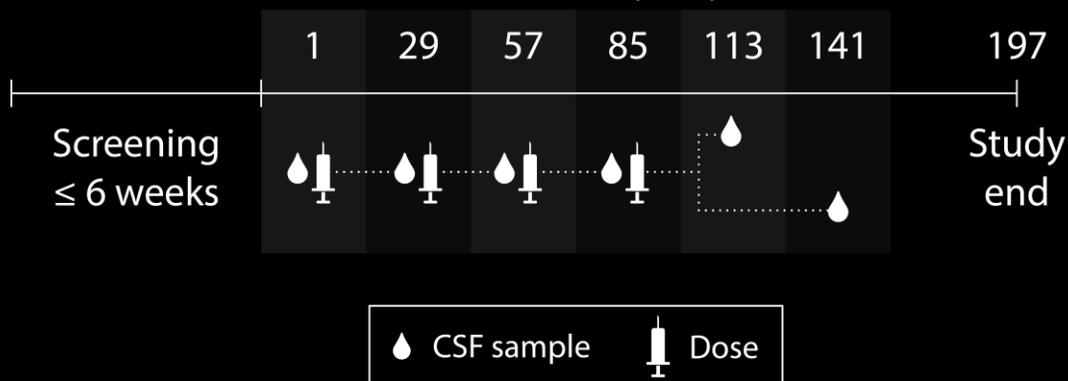
Pharmacokinetics in CSF

Exploratory objectives

- CSF mHTT
- PK in plasma
- Clinical outcomes
Fluid biomarkers, MRI, EEG

Participants Stage 1 HD, TFC 11-13		IONIS-HTT _{Rx} N=34	Placebo N=12
Age	mean (SD) range	46 (10) 26 - 65	49 (10) 31 - 65
Gender	male / female %	20 / 14 59% / 41%	8 / 4 67% / 33%
CAG repeats	mean (SD) range	44 (3) 40 - 55	44 (2) 41 - 50

Study day

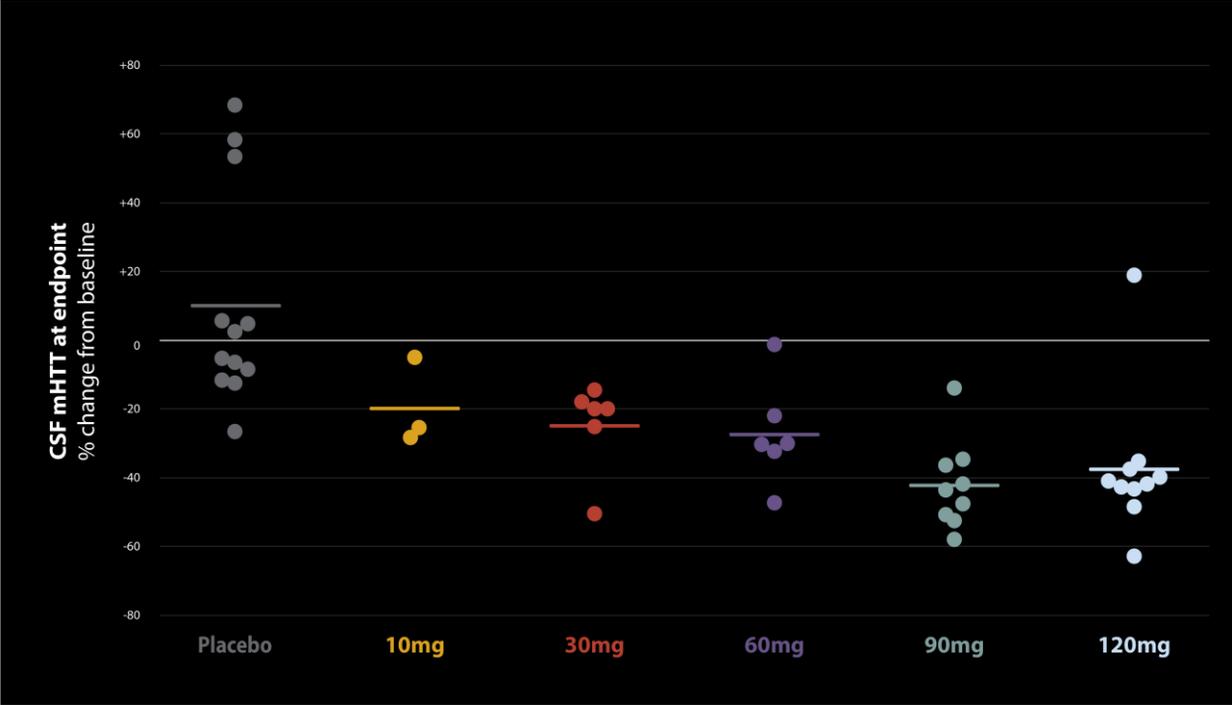
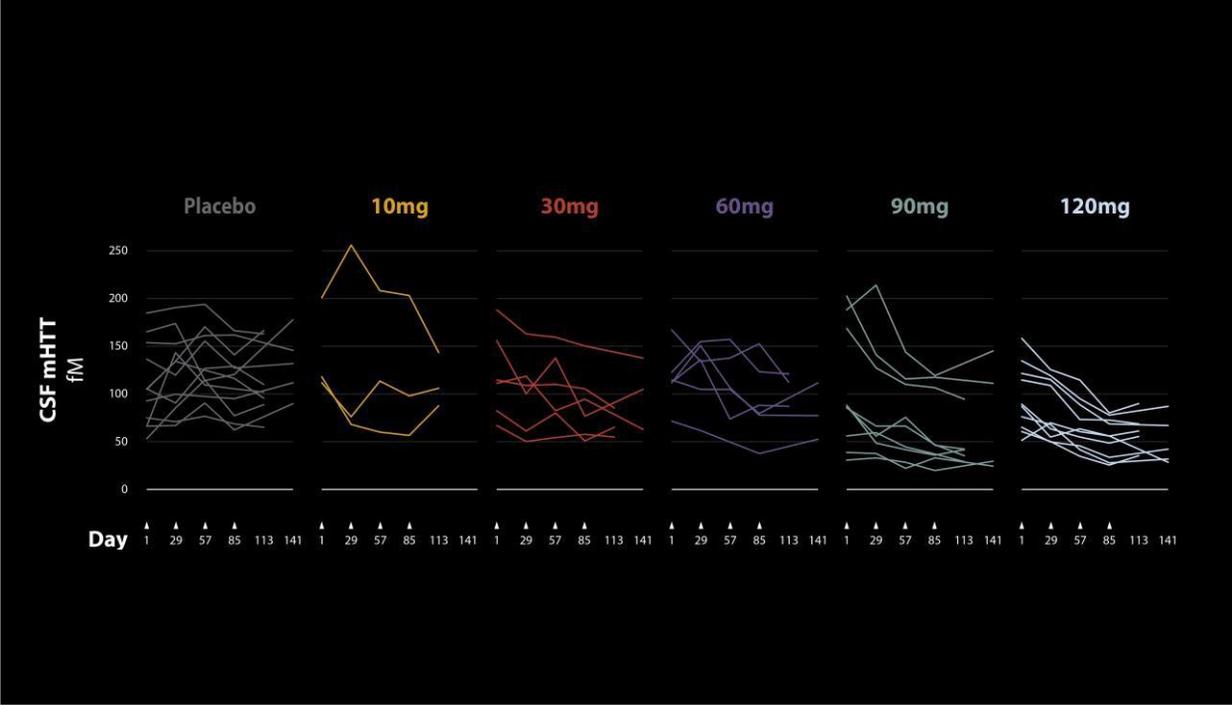


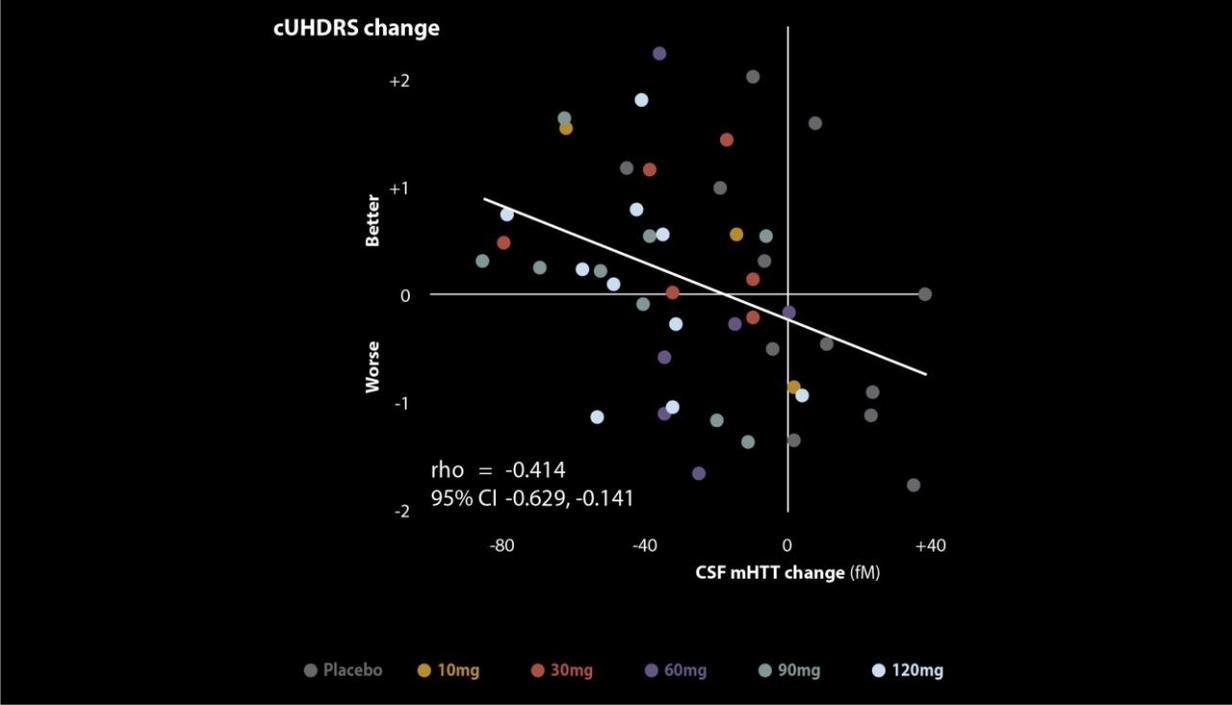


September
2015

Safety

- Well-tolerated
- No participants discontinued
- Most AEs mild and unrelated to study drug
- Post-LP headaches after about 10% of LPs; no blood patches
- No serious adverse events in active treatment groups
- One SAE event in a placebo-treated patient
 - Mild post-lumbar puncture headache, hospitalized for observation, no sequelae
- No clinically meaningful changes in safety laboratory parameters



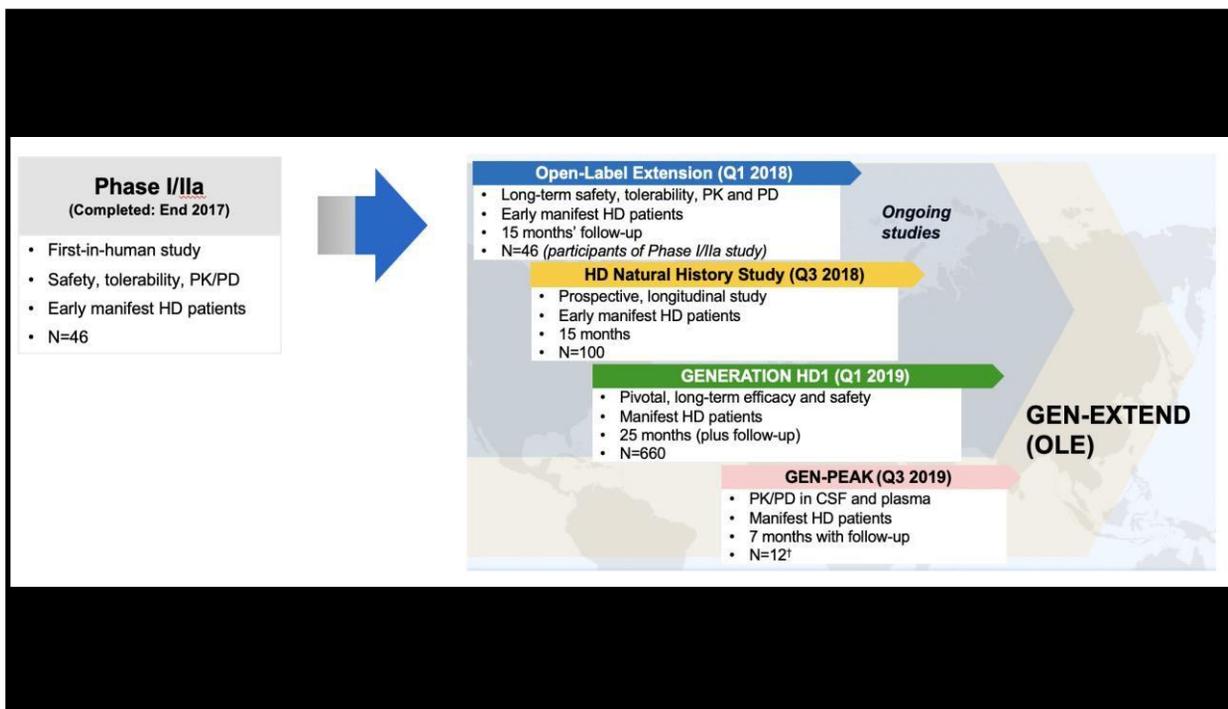


The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting Huntingtin Expression in Patients with Huntington’s Disease

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HTTRx / RG6042 Acknowledgements

- Patients and families who participated in the study
- HTTRx Principal Investigators and their teams
 - Sarah Tabrizi, University College London, London, UK
 - Roger Barker, Cambridge University, Cambridge, UK
 - David Craufurd, University of Manchester, Manchester, UK
 - Bernhard Landwehrmeyer, Ulm University, Ulm, Germany
 - Blair Leavitt, University of British Columbia, Vancouver, BC, Canada
 - Josef Priller, Charité University, Berlin, Germany
 - Hugh Rickards, University Hospitals, Birmingham UK
 - Anne Rosser, University Hospital of Wales, Cardiff, UK
 - Carsten Saft, Ruhr-University Bochum, Bochum, Germany
- Ionis colleagues
 - Special thanks to Frank Bennett, Holly Kordasiewicz, Anne Smith, Roger Lane, Dan Norris Tom Zanardi, Erika Paz, Tiffany Baumann, Kristin Balogh, Eric Swayze and Scott Henry
- Roche colleagues
 - Special thanks to Scott Schobel, Christian Czech and Irene Gerlach
- CHDI, Doug Macdonald, Don Cleveland, Vincenzo Libri

