

# Results from SELECT-HD: An allele-selective mutant huntingtin-lowering approach in Huntington's Disease

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## Disclosures

- Jane Atkins is an employee of Wave Life Sciences

## Results from SELECT-HD

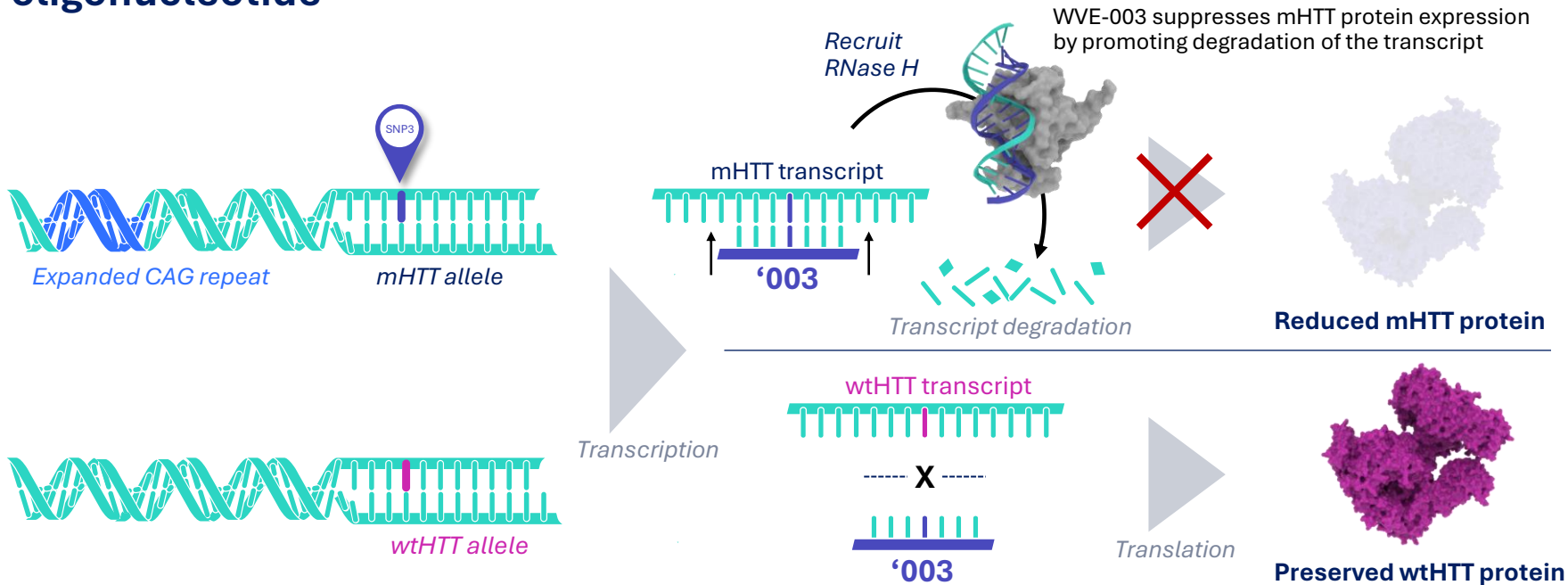
**WVE-003\* exceeded our predefined criteria for  $\geq 30\%$  CSF mHTT lowering**

**Confirmed WVE-003's allele-selective, wild-type HTT sparing mechanism of action**

**30 mg Q8W regimen had a safe and tolerable profile**

**First demonstrated association between mHTT lowering and slowing of caudate atrophy**

# WVE-003: First-in-class investigational allele-selective, mHTT lowering oligonucleotide



Preclinical data published in *Molecular Therapy Nucleic Acids*

# SELECT HD : Adaptive Ph1b/2a randomized, placebo controlled, double-blind clinical trial designed to rapidly assess WVE-003 in HD

## Key eligibility criteria

- CAG >36
- SNP3 on mHTT allele
- ≥25 to ≤60 years old
- TFC >9
- DCL = 4

## Single-ascending dose phase

## Multidose phase

	30, 60, 90 mg single doses & follow-up (1:2 random)					30 mg Q8W & follow-up (vs placebo)							
Day(s)	1-3	15	29	57	85	1	29	57	85	113	141	169	197
Dose	●					●		●		●			
CSF samples	●	●	●	●	●	●	●	●	●	●	●	●	●
Clinical evaluations	●				●	●				●		●	
MRI	●					●						●	

## Key objectives

- Safety and tolerability
- Plasma & CSF PK profile
- CSF biomarkers (mHTT, wtHTT, NfL)
- Exploratory clinical assessments
- Exploratory MRI

## Key study adaptations

- ❖ Expanded single-dose cohorts
- ❖ Initiated 30 mg Q8W multi-dose cohort

## Baseline characteristics were generally balanced across cohorts

Category	Single Dose				Multidose	
	Placebo (N=16)	30 mg (N=13)	60 mg (N=10)	90 mg (N=8)	Placebo (N=7)	30 mg (N=16)
Age at diagnosis (years), mean	38.81	42.31	39.60	45.25	37.43	41.88
<b>Sex, n (%)</b>						
Male	10 (62.5)	7 (53.8)	7 (70.0)	5 (62.5)	5 (71.4)	11 (68.8)
Female	6 (37.5)	6(46.2)	3 (30.0)	3 (37.5)	2 (28.6)	5 (31.3)
<b>CAG repeat length</b>						
Mean (SD)	43.8 (2.1)	42.2 (1.7)	45.2 (4.1)	44.5 (1.2)	45 (2.5)	43.5 (2.5)
Min, Max	41, 48	40, 45	40, 54	43, 47	41, 48	40, 48
<b>HD-ISS Stage n (%)</b>						
Stage 0	1 (6.3)	1 (7.7)	0	0	0	0
Stage 1	0	0	0	0	0	0
Stage 2	4 (25.0)	1 (7.7)	2 (20.0)	1 (12.5)	0	3 (18.8)
Stage 3	11 (68.8)	11 (84.6)	8 (80.0)	7 (87.5)	7 (100)	13 (81.3)

# Multidose safety: 30 mg WVE-003 was generally safe and well tolerated

## WVE-003

Category	Placebo n=7 (%) [# events]	30 mg n=16 (%) [#events]
Patients with at least one TEAE	7 (100) [25]	13 ( 81.3) [53]
Mild	5 ( 71.4)	6 ( 37.5)
Moderate	2 ( 28.6)	7 ( 43.8)
Severe	0	0
Patients with TEAE related to study drug	0	8 ( 50.0) [20]
Mild	0	3 ( 18.8)
Moderate	0	5 ( 31.3)
Severe	0	0
Patients with severe TEAE related to study drug	0	0
Patient with serious TEAE	0	0
Patients with a serious TEAE related to study drug	0	0

## Safety Summary

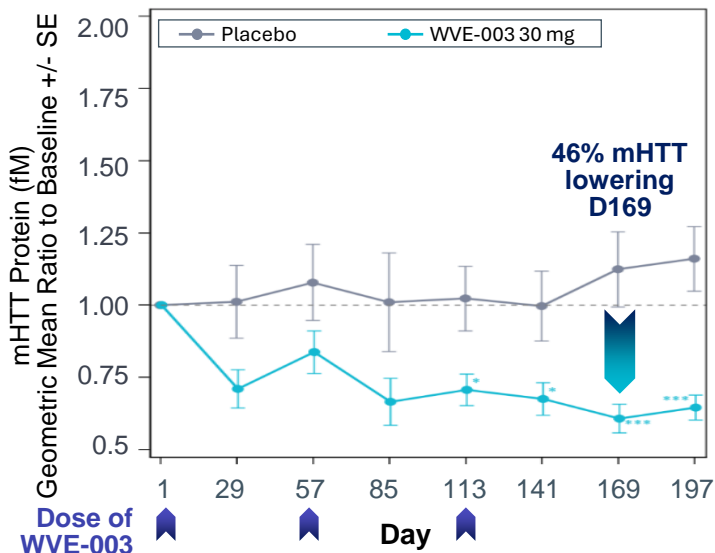
- **30 mg WVE-003:** all AEs mild or moderate in intensity
- AEs balanced across cohorts for single & multidose phases
- **Single-dose phase:** one severe & one serious AE in placebo; one serious AE in 60 mg; one severe AE leading to withdrawal in 90 mg
- **Multidose phase:** No SAEs; imbalance in treatment-related AEs (all mild or moderate)
- No statistically significant elevations in CSF WBCs
- Ventricular volume changes were consistent with natural history; no cases of hydrocephalus



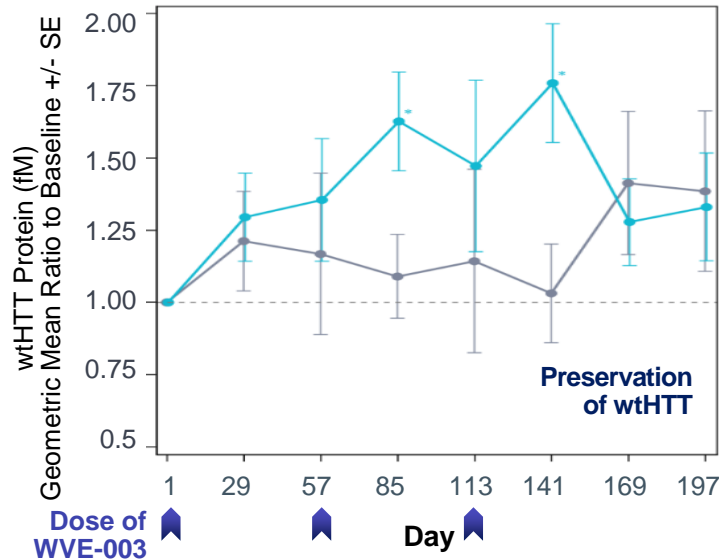
# Multiple doses of WVE-003 demonstrated selective, potent, and durable reduction of mHTT

Poster J005

## CSF mHTT protein levels



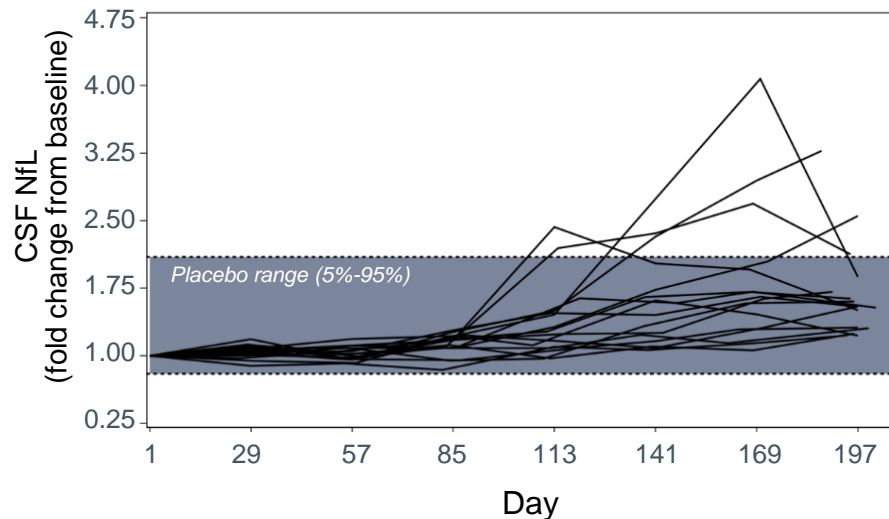
## CSF wtHTT protein levels



Durability of mHTT reductions and PK-PD modeling support quarterly dosing interval

# Some CSF NfL elevations observed

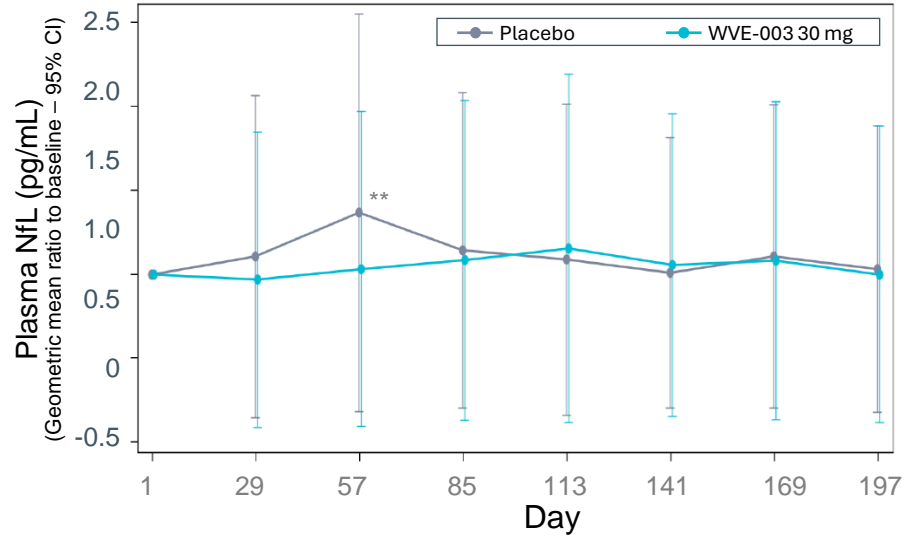
## CSF NfL



**CSF NfL changes not correlated with severity or number of AEs, change in caudate volume**

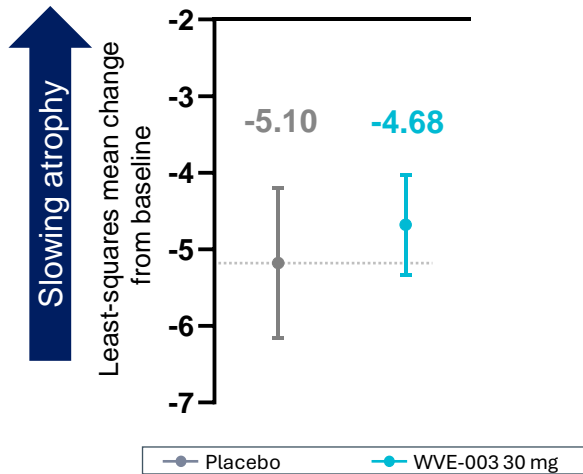
# There was a disconnect in NfL changes between plasma and CSF

## Plasma NfL

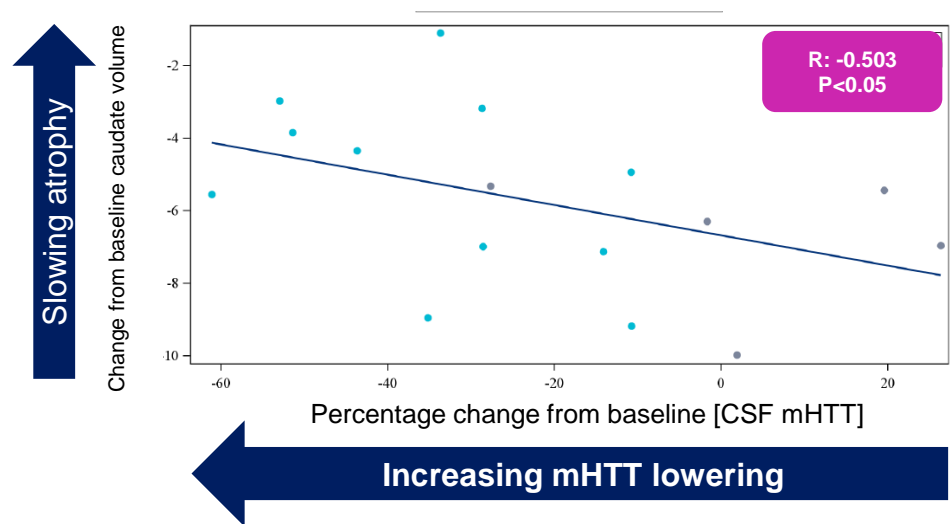


# Slowing of caudate atrophy associated with mHTT lowering, WVE-003 exposure

## Normalized caudate volume

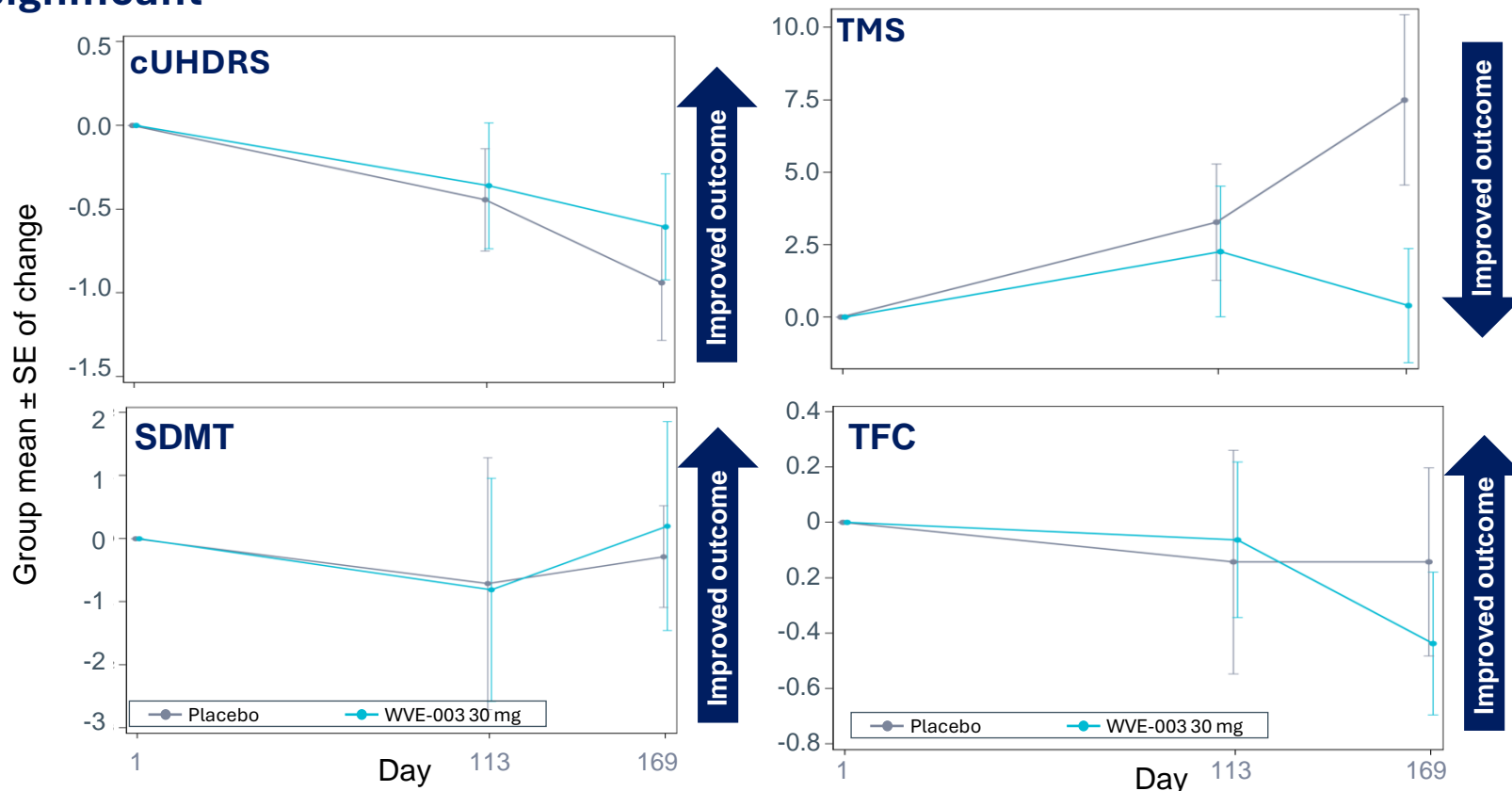


## mHTT lowering associated with slowing caudate atrophy



Similar association observed between slowing atrophy and increasing WVE-003 CSF concentration

# Some exploratory clinical measures favored WVE-003, not statistically significant



*SELECT-HD was not powered to show significant changes in clinical measures*

## Summary of SELECT-HD results

- 30 mg WVE-003 dosed every 8 weeks was generally safe and well-tolerated
  - AEs all mild or moderate, no SAEs
  - Changes in ventricular volume were in line with natural history cohort
- mHTT lowering, wtHTT sparing achieved criteria for advancement of WVE-003
  - Mean mHTT reductions up to 46% compared with placebo (P=0.0007)
  - Durable mHTT reduction, with mean 44% lowering maintained for at least 12 weeks after dosing
  - wtHTT levels were preserved throughout single and multidose phases
  - Single, multidose data & modeling support quarterly dosing
- First demonstration of mHTT lowering associated with slowing caudate atrophy
  - Slowing of degeneration of a deep brain region (caudate) observed
  - Significant associations between slowing degeneration and mHTT lowering, WVE-003 exposure
  - Some exploratory clinical measures favored WVE-003 over placebo (e.g., TMS)

**THANK YOU** to **SELECT-HD** participants and their families

## Clinical Advisory Committee

- Daniel Claassen
- Mary Edmondson
- Ray Dorsey
- Ralf Reilmann

## Collaborators

- Asuragen
- Evotec
- CHDI
- IXICO
- EHDN
- Enroll-HD

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- Katie Youssef

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