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SELECT-HD Clinical Trial Results

Investor Presentation

June 25, 2024

Forward-looking statements

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Today's agenda

Opening remarks
Paul Bolno, MD, MBA
President and CEO

WVE-003: First-in-class allele-selective candidate for HD
Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS
Chief Development Officer

SELECT-HD clinical trial results
Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS
Chief Development Officer

Anticipated upcoming milestones and closing remarks
Paul Bolno, MD, MBA
President and CEO

Positive results from SELECT-HD trial: First clinical demonstration of allele-selective silencing

PRISM Platform

- Proprietary chemistry enhances potency, durability, specificity
- Preclinical models to inform clinical development
- Leveraging leadership in SNP and biomarker development

Robust Clinical Translation

- ✓ Potent and durable mHTT reductions of up to 46% with multiple doses of 30 mg of WVE-003; generally safe and well tolerated
- ✓ Preservation of healthy, wild-type HTT (allele selectivity)
- ✓ Ventricular volume in line with natural history
- ✓ Statistically significant correlation of mHTT reduction with slowing of caudate atrophy, an imaging biomarker that is predictive of clinical outcomes
- ✓ Point estimates favored WVE-003 on Total Motor Score (TMS)

mHTT: mutant huntingtin protein, wtHTT: wild-type huntingtin protein

WVE-003: First-in-class allele-selective candidate for HD

Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS

Chief Development Officer

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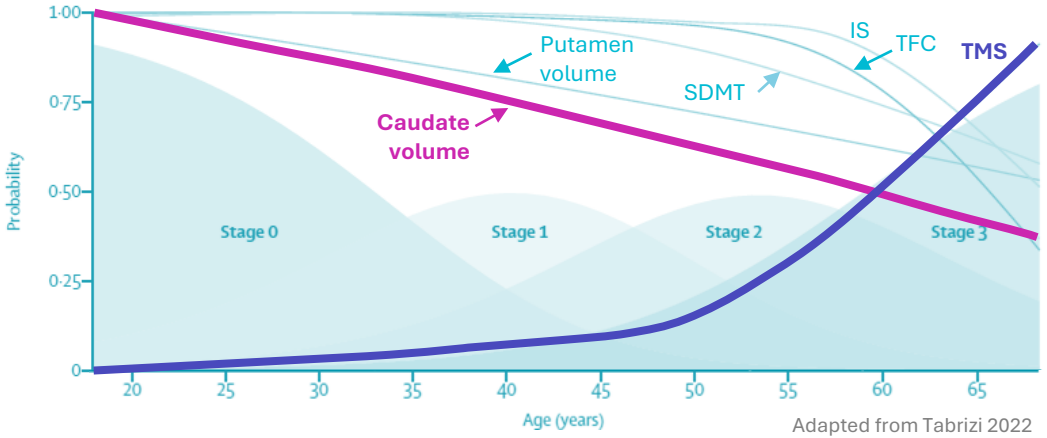
Huntington's disease is a devastating neurological disorder caused by a toxic gain of function and concurrent loss of function

- HD is a monogenic autosomal dominant genetic disease; fully penetrant and affects entire brain
- Characterized by cognitive decline, psychiatric illness, and chorea; ultimately fatal
- Expanded CAG triplet repeat in *HTT* gene results in production of mutant huntingtin protein (mHTT) and loss of function in wild-type huntingtin protein (wtHTT)
- wtHTT is critical for normal neuronal function

HD-ISS stage probability and predicted clinical landmark changes as a function of age



Adapted from Tabrizi 2022

Pre-Symptomatic HD
(~160K in US and Europe)

Symptomatic HD
(~65K in US and Europe)

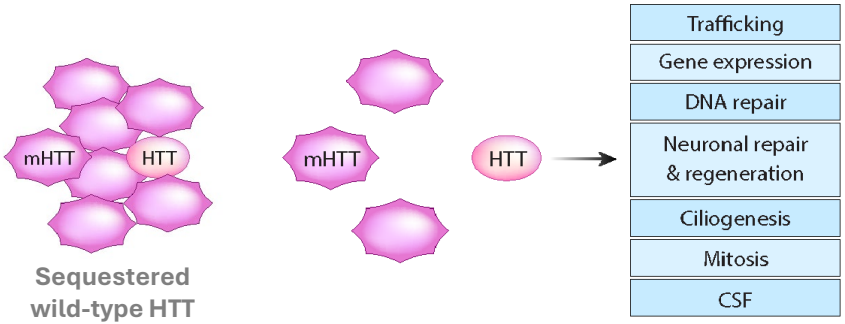
An allele-selective, wtHTT-sparing approach is uniquely suited to address HD across all stages of disease

Sources on wtHTT: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 2010 13. Smith-Dijak 2019 14. Tousley 2019 15. Zhang 2018 16. McAdam 2020 17. Altar 1997 18. Zuccato 2001 19. Gauthier 2004 20. Ferrer 2000 21. Baquet 2004 22. Liu 2011 23. Karam 2015; IS, Independence Scale; SDMT, Symbol Digit Modalities Test; TFC, Total Functional Capacity; TMS, Total Motor Score

Wild-type HTT (wtHTT) is critical for normal neuronal function and loss of wtHTT contributes to cellular dysfunction

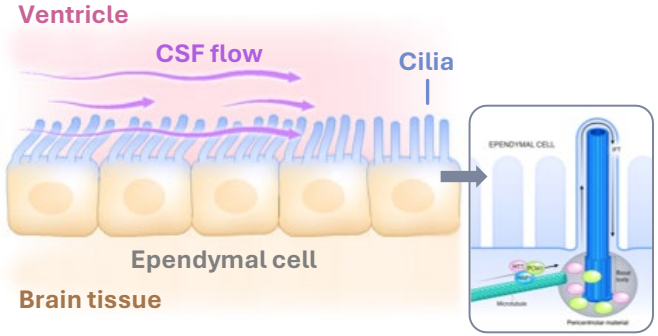
Mutant HTT has a detrimental effect on wild-type HTT function

- Lowering mHTT is expected to restore physiological control over HTT gene expression and relieve its detrimental effect on wtHTT function



Wild-type HTT is crucial for cilia health

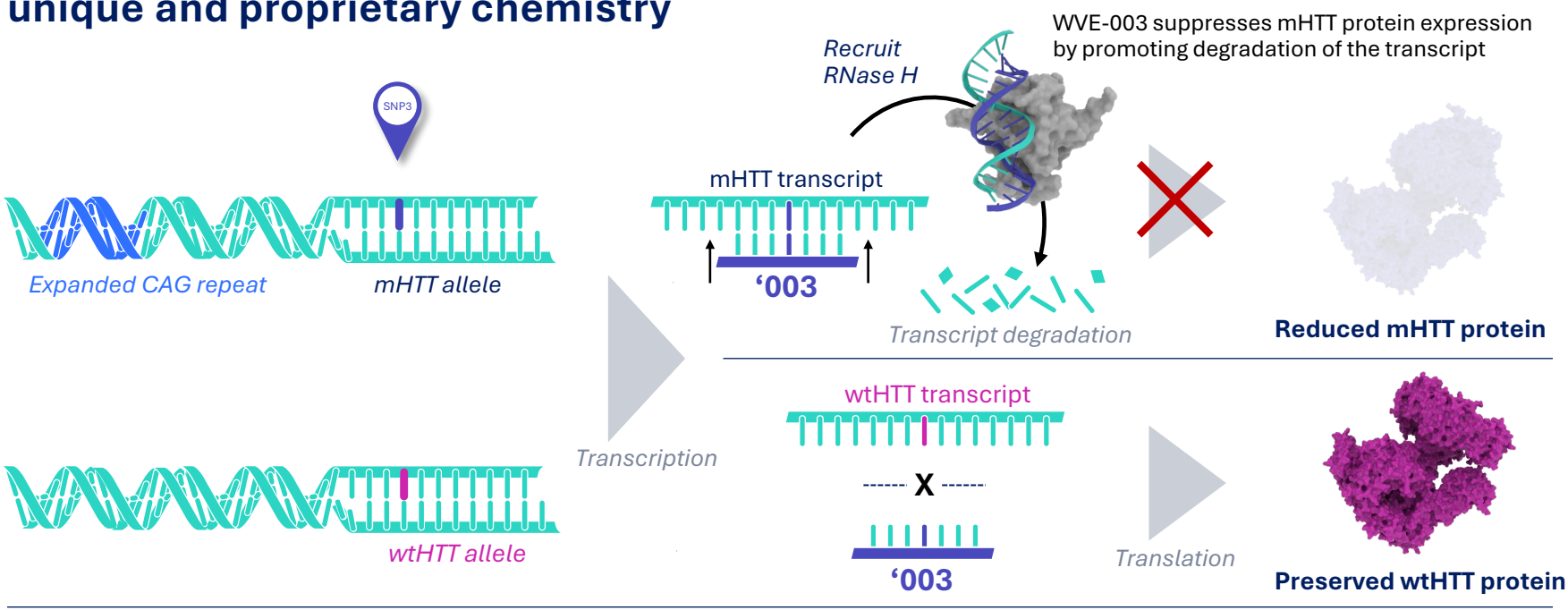
- In the absence of wtHTT, ciliogenesis fails, disrupting CSF flow, causing hydrocephalus



Only an allele-selective approach can ameliorate both loss-of-function and gain-of-function disruptions driven by mHTT

Saudou & Humbert 2016 Neuron; Cason et al., 2022 Nat Rev Cell Biol; Laundos et al., 2023 Front Cell Dev Biol; Kaliszewski et al., 2015 Cell Death Diff; Keryer et al., 2011 J Clin Invest
Khoshnan & Patterson, 2011. Neurobiol Dis; Pogoda et al., 2021 Curr Med Chem; Hsiao et al., 2013 Hum Mol Genet

WVE-003: First-in-class allele-selective oligonucleotide, enabled by Wave's unique and proprietary chemistry



Molecular Therapy Nucleic Acids

Preclinical data published in *Molecular Therapy Nucleic Acids*

Successful translation to clinic

Iwamoto *et al.*, *Mol Ther Nuc Acids* 2024 DOI: 10.1016/j.omtn.2024.102246

SELECT-HD clinical trial results

Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS
Chief Development Officer

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SELECT-HD clinical trial designed to demonstrate mHTT reduction, wtHTT preservation, safety and tolerability

Key objectives of the SELECT-HD clinical trial of WVE-003 were to demonstrate:

- Potent, selective and durable mHTT reductions of >30% in CSF
- Allele-selectivity, preservation of wtHTT
- Safety and tolerability
- Pharmacokinetics

Exploratory objectives included evaluation of caudate atrophy and functional measures

Study was not powered to detect clinical effects

Planned clinical assessments:

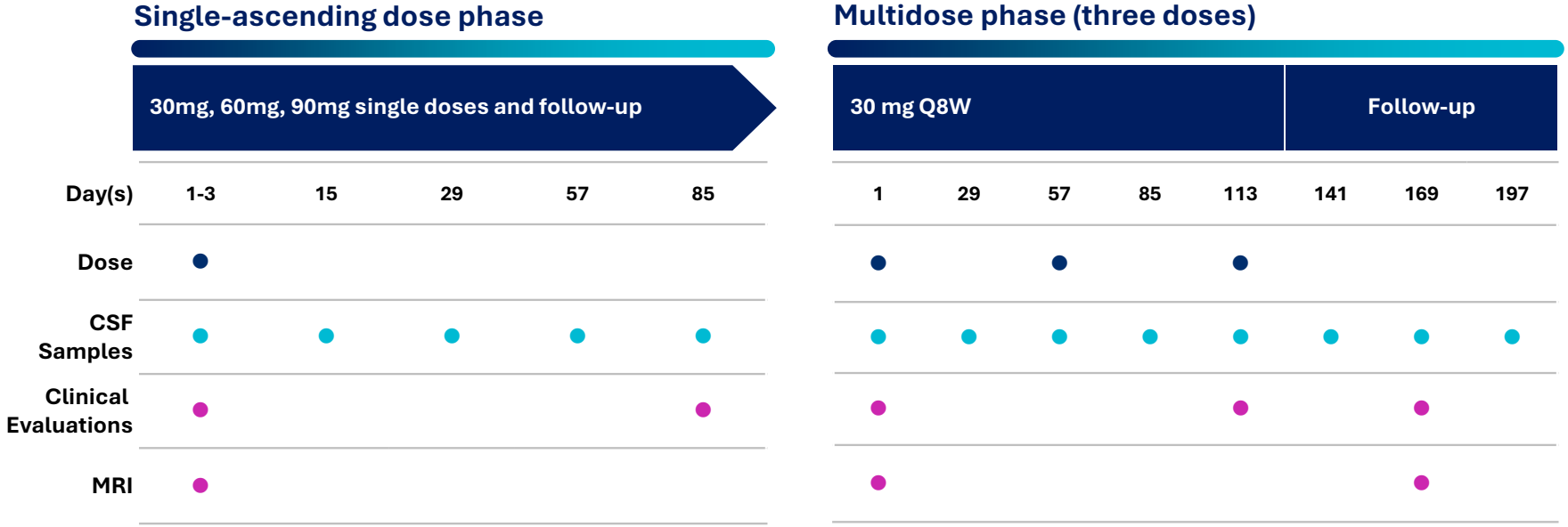
- vMRI to assess caudate atrophy – an imaging biomarker that is predictive of clinical outcomes
- Clinical measures (TMS, TFC, SDMT, Stroop, cUHDRS)

Liu et al., 2023 Brain Comm

Clinical trial designed to assess allele-selective mHTT knockdown with WVE-003

SELECT HD

Phase 1b/2a global, multicenter, randomized, double-blind, placebo-controlled trial in people living with HD, with SNP3 on mHTT allele and between ≥25 to ≤60 years old



SELECT-HD trial was designed to rapidly optimize dose level and frequency based on early indicators of target engagement and safety

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 (years) mean	38.81	42.31	39.60	45.25	37.43	41.88
Gender, n (%)						
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)
CAG length						
Mean (SD)	43.8	42.2	45.2	44.5	45	43.5
Min-Max	41, 48	40, 45	40, 54	43, 47	41, 48	40, 48
HD-ISS Stage n (%)						
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)

Safety and tolerability

Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS
Chief Development Officer

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Single dose safety: 30 mg WVE-003 was generally safe and well tolerated

Category	Placebo n=16 subjects (%)	WVE-003 30 mg n=13 subjects (%)	WVE-003 60 mg n=10 subjects (%)	WVE-003 90 mg n=8 subjects (%)
Patients with at least one TEAE	13 subjects [51 events]	9 subjects [30 events]	8 subjects [22 events]	8 subjects [54 events]
Mild	8 (50.0)	7 (53.8)	7 (70.0)	5 (62.5)
Moderate	4 (25.0)	2 (15.4)	1 (10.0)	2 (25.0)
Severe	1 (6.3)	0	0	1 (12.5)
Patients with TEAE related to study drug	2 (12.5)	1 (7.7)	3 (30.0)	3 (37.5)
Mild	1 (6.3)	1 (7.7)	2 (20.0)	1 (12.5)
Moderate	1 (6.3)	0	1 (10.0)	1 (12.5)
Severe	0	0	0	1 (12.5)
Patients with severe TEAE related to study drug	0	0	0	1 (12.5)
Patient with serious TEAE	1 (6.3)	0	1 (10.0)	0
Patients with a serious TEAE related to study drug	0	0	1 (10.0)	0
Patients withdrawing due to TEAE related to study drug	0	0	0	1 (12.5)

Multidose safety: All AEs in subjects receiving WVE-003 were mild or moderate in intensity

Category	Placebo (n=7) [# events]	WVE-003 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
Patients withdrawing due to TEAE related to study drug in P1	0	0

Ventricular volume (vMRI) consistent with natural history

mHTT silencing and wtHTT preservation

Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS
Chief Development Officer

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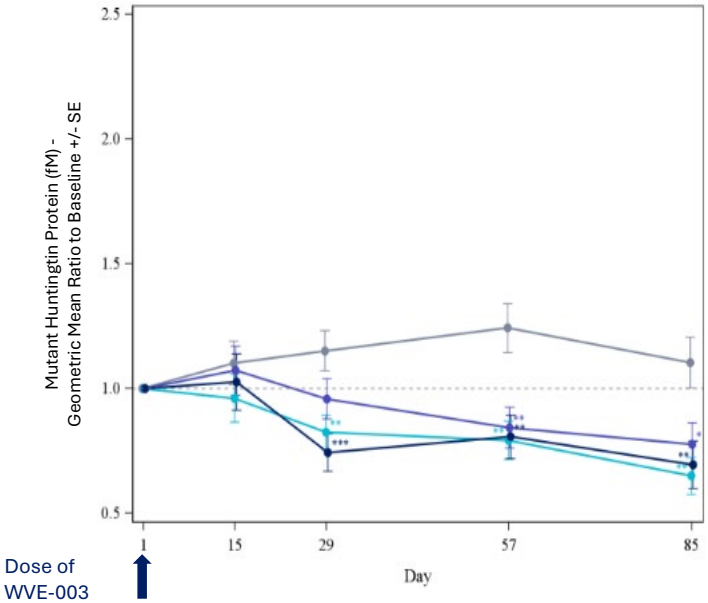
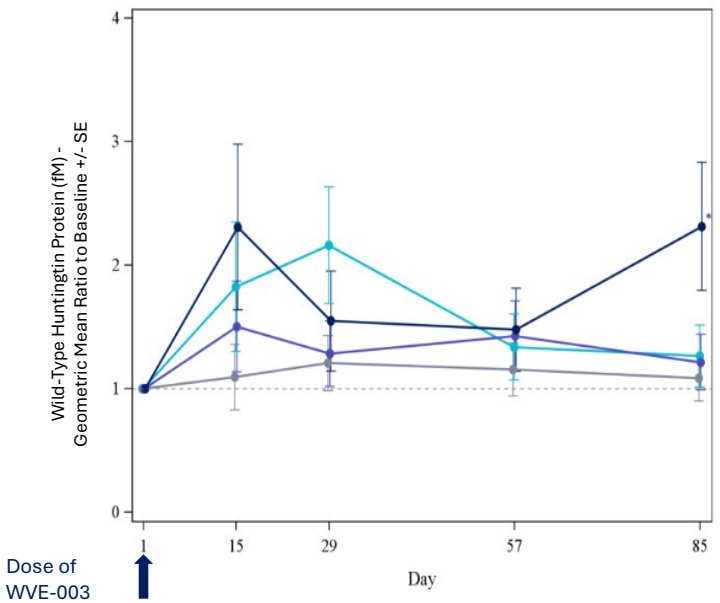
Single doses of WVE-003 led to robust, durable mHTT silencing and wtHTT preservation, with effects persisting at 12 weeks

mHTT protein levels



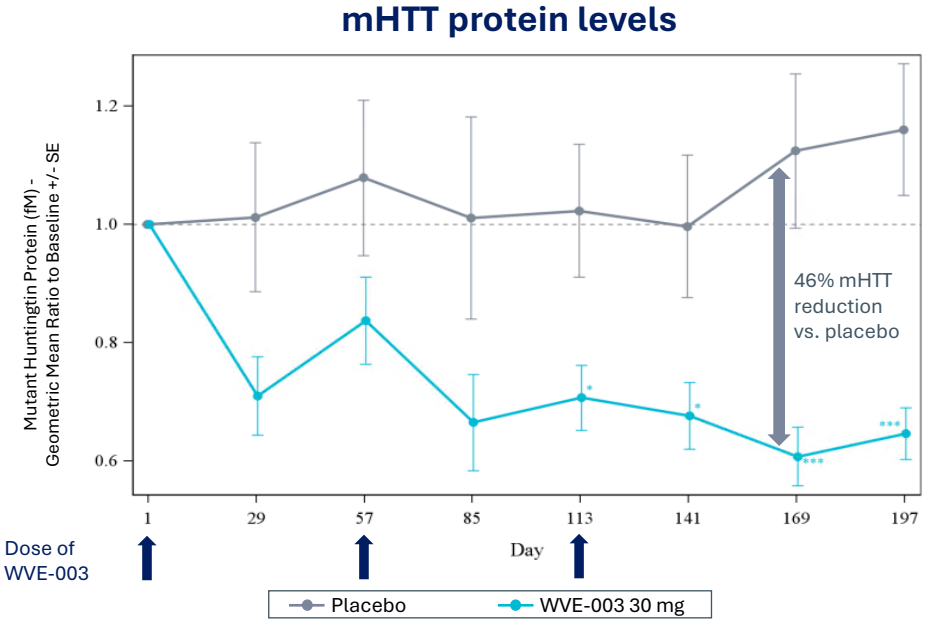
wtHTT protein levels



Placebo
WVE-003 30 mg
WVE-003 60 mg
WVE-003 90 mg

* p<0.05, **p<0.01, ***p<0.001, ****p<0.0001
mHTT: mutant huntingtin protein; wtHTT: wild-type huntingtin protein

Multiple (three) doses of WVE-003 demonstrate selective, potent, and durable reduction of mHTT in SELECT-HD



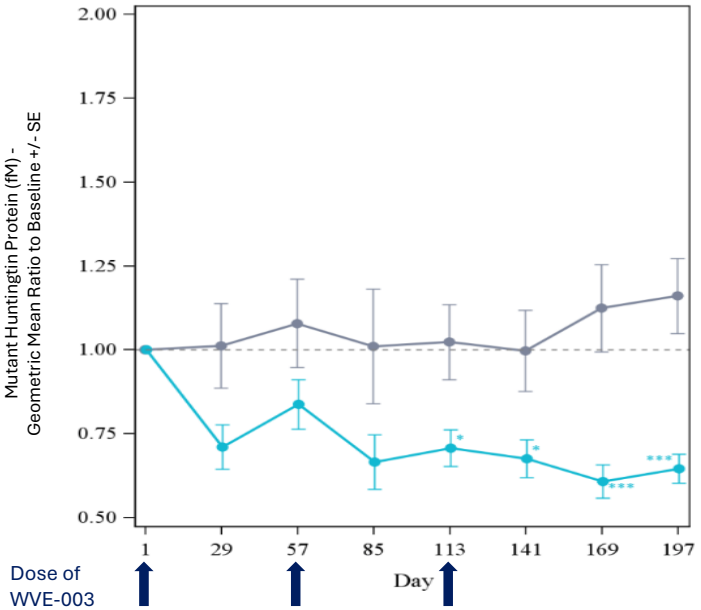
- At Day 169 (8 weeks post-last dose), mHTT reduction of 46% vs. placebo (P=0.0007)
- mHTT reduction was durable (44% vs. placebo; P=0.0002) out to 12 weeks post-last dose (Day 197)

Durability of mHTT reductions supports potential for quarterly dosing intervals

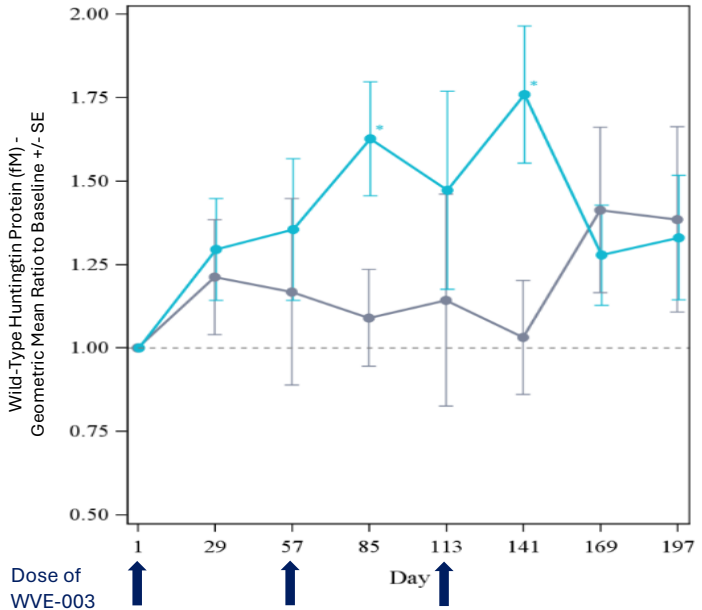
* p<0.05, **p<0.01, ***p<0.001, ****p<0.0001
mHTT: mutant huntingtin protein; wtHTT: wild-type huntingtin protein

Allele-selective lowering of mHTT protein with WVE-003 and preservation of wild-type HTT (wtHTT)

mHTT protein levels



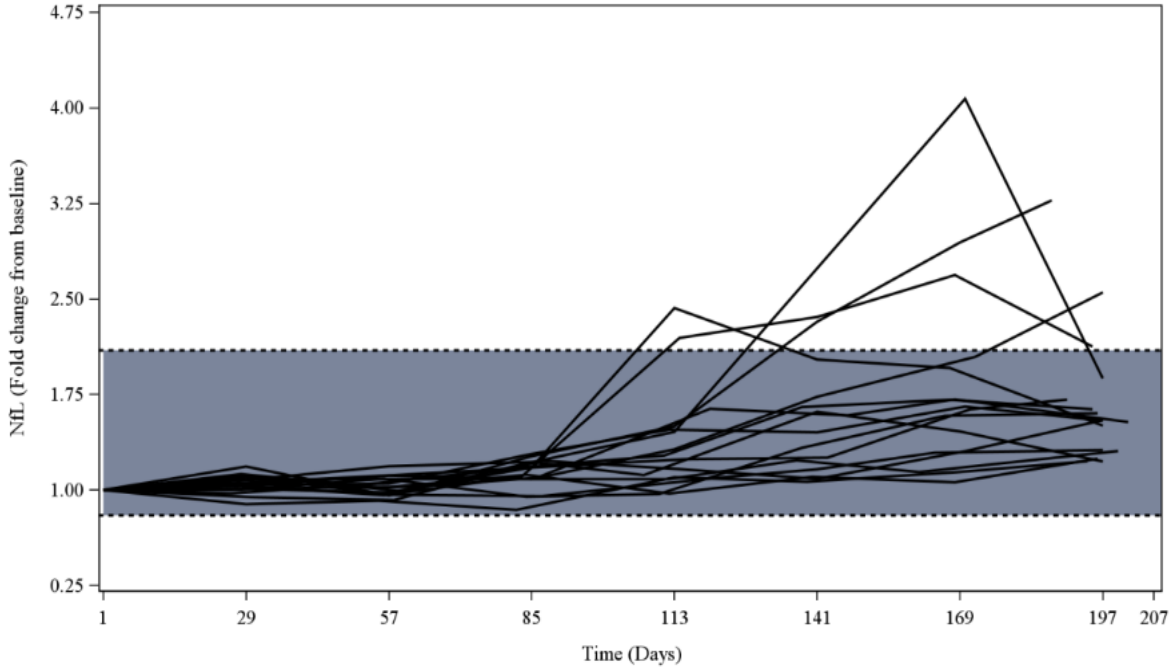
wtHTT protein levels



Placebo — WVE-003 30 mg

* p<0.05, **p<0.01, ***p<0.001, ****p<0.0001
mHTT: mutant huntingtin protein; wtHTT: wild-type huntingtin protein

CSF neurofilament light protein (NfL) elevations were in line with placebo for the majority of WVE-003-treated participants



NfL levels from placebo arm are represented in gray area (5-95th percentiles)

Exploratory clinical measures and regulatory next steps

Anne-Marie Li-Kwai-Cheung, MChem, MTOPRA, RAPS

Chief Development Officer

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WVE-003 leads to allele-selective mHTT reduction, correlating with slowing of caudate atrophy

Allele-Selective mHTT KD with wtHTT Preservation

- mHTT reduction of up to 46% vs. placebo
- wtHTT preserved/increased throughout study

Slowing of Caudate Atrophy

- WVE-003 trended towards less caudate atrophy vs. placebo (4.68% vs. 5.10%, not significant)

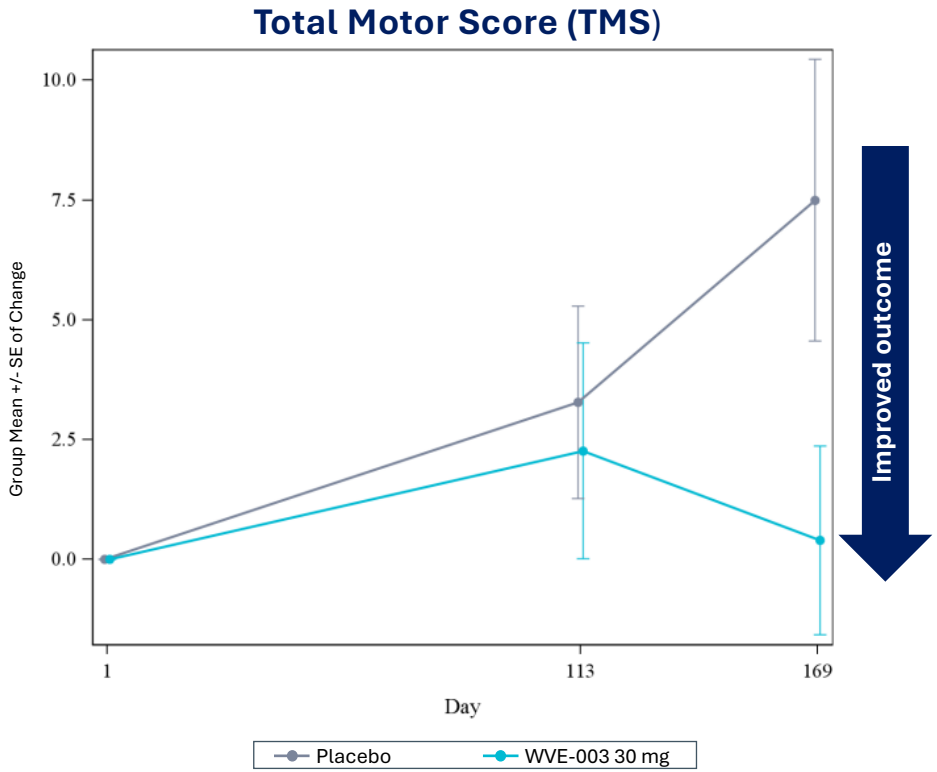
Functional Benefit

- Caudate atrophy is an imaging biomarker expected to predict clinical outcomes, including clinically meaningful worsening of Total Motor Score (TMS)

Greater allele-selective mHTT reduction correlated with the slowing of caudate atrophy at 24 weeks (R = -0.50, p=0.047)

Liu et al., 2023 Brain Comm

Clinical measures favor WVE-003 in Total Motor Score



WVE-003: First-in-class allele-selective investigational therapeutic with potential best-in-class profile for Huntington's disease

- ✓ Significant, selective, and durable mHTT reductions of 46% in CSF
- ✓ Preservation of wild-type HTT
- ✓ Ventricular volume consistent with natural history
- ✓ mHTT reductions correlated with slowing of caudate atrophy

Multiple doses of WVE-003 were generally safe and well-tolerated

Preservation of caudate volume offers an efficient pathway for potential accelerated approval for HD

Draft study design:

Registrational study powered to show impact on caudate atrophy

- Randomized, placebo controlled clinical study
  Adults with SNP3 and HD Stage 1-2
- N = ~150
- 12-18 months duration

Plan to engage regulators on path to accelerated approval before year-end 2024

vMRI: volumetric MRI

Anticipated upcoming milestones and closing remarks

Paul Bolno, MD, MBA,

President and CEO

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Continued translation in the clinic reinforces broader value of Wave pipeline, with multiple additional near-term milestones

Wave's Platform Has Translated in the Clinic

WVE-003
HD
ASO Silencing

- ✓ Potent and durable target engagement
- ✓ First-ever clinical demonstration of allele-selective silencing

WVE-N531
DMD
Splicing

- ✓ High muscle concentrations and highest reported exon skipping at six weeks

Additional Near-Term Milestones

WVE-N531
DMD
Splicing

- Potentially registrational 24-week dystrophin data from FORWARD-53 expected 3Q 2024

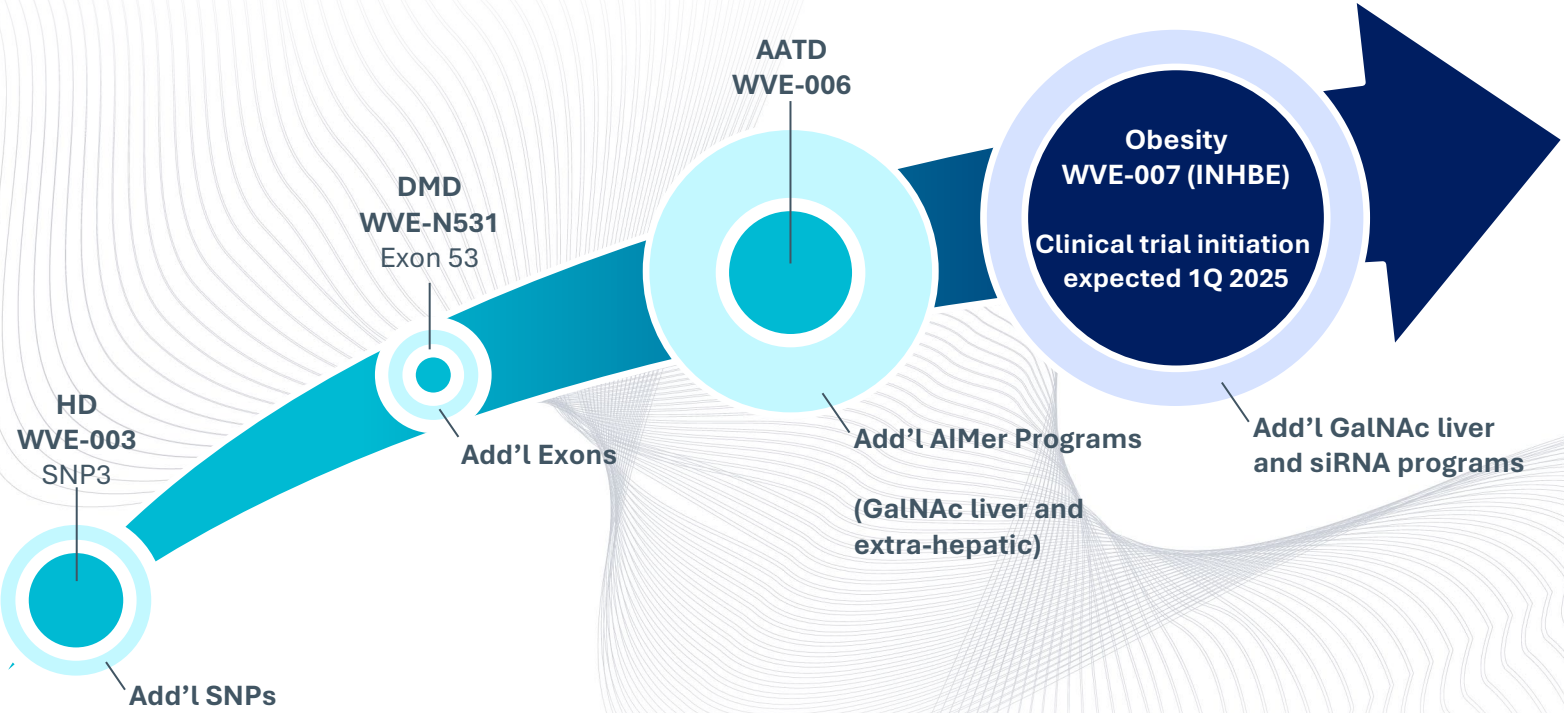
WVE-006
AATD
GalNAc-RNA Editing

- Proof-of-mechanism data expected from RestorAATion-2 expected in 2024

WVE-007 (INHBE)
Obesity
GalNAc-siRNA

- Expect to initiate clinical trial in Q1 2025

Wave is poised for significant and sustained growth



Wave's platform is translating in the clinic, with DMD and AATD data updates expected in 2024 and advancement of WVE-007 (INHBE)

Note: Bubble size illustrative of size of total addressable US market (assuming 100% share of addressable patients)

Q&A

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For questions contact:
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