SELECT-HD: an adaptive first-in-human clinical trial to evaluate WVE-003, an investigational allele selective mHTT-lowering oligonucleotide, in early manifest Huntington's disease

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HSG: Nov 5, 2021

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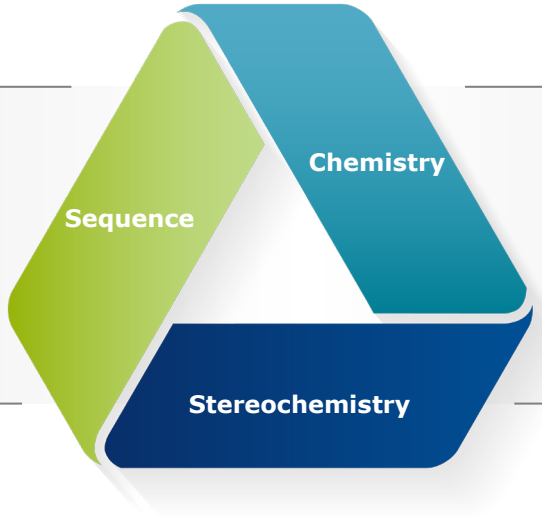
PRISM Unlocking the body's own ability to treat genetic disease

DESIGN

Unique ability to construct stereopure molecules and control three structural features of oligonucleotides to efficiently engage biological machinery



OPTIMIZE

Provides the resolution to observe this structural interplay and understand how it impacts key pharmacological properties

Built-for-Purpose Candidates to Optimally Address Disease Biology

Silencing | Splicing | RNA Editing

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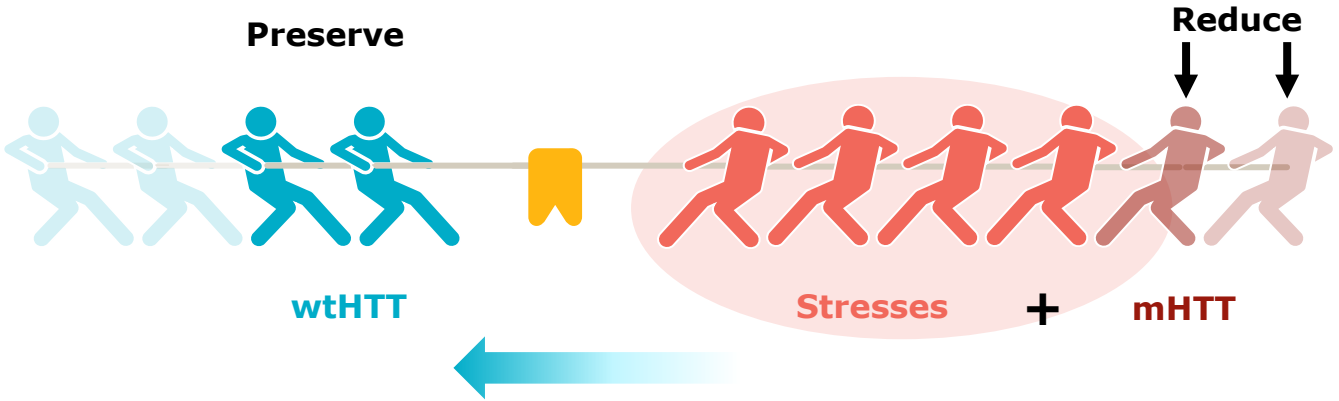
Allele-selective approach to treating HD

Preserve neuroprotective effects of wildtype HTT and reduce toxic mutant HTT



wtHTT supports healthy brain function, especially in the context of stress

Promotes neuronal survival

Essential role in synaptic protein transport

Supplies BDNF to striatum to regulate synaptic plasticity

Critical role in cilia function underlying CSF circulation needed to clear catabolites & maintain homeostasis

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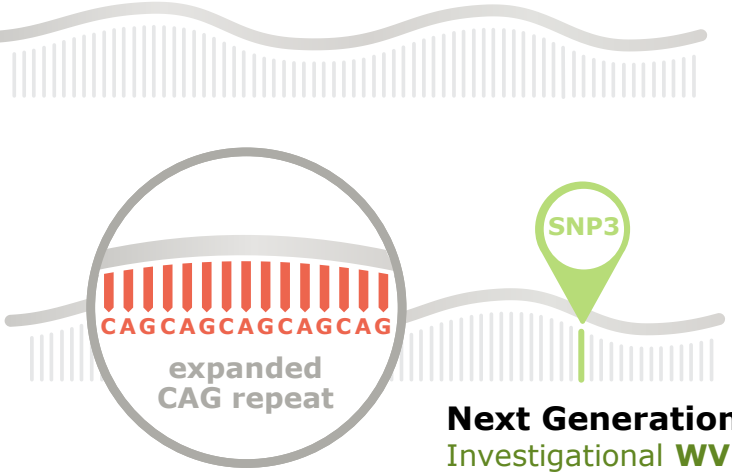
mHTT, mutant HTT; wtHTT, wild-type HTT; CSF: cerebrospinal fluid; BDNF, brain-derived neurotrophic factor Sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. 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, 24. Menalled et al., 2009

Allele-selectivity achieved by targeting downstream SNPs

Target mHTT transcript to selectively reduce mHTT protein with antisense oligonucleotides

Wildtype huntingtin RNA

Mutant huntingtin RNA



Next Generation Chemistry
Investigational **WVE-003** targets mHTT "SNP3"

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mHTT, mutant huntingtin; SNP, single nucleotide polymorphism

Introducing WVE-003, an investigational allele-selective oligonucleotide

Contains new chemistry with potential to address limitations of first-generation molecules

- ✓ Allele-selective approach designed to lower mutant HTT & preserve wildtype HTT
- ✓ New PN chemistry has demonstrated enhanced potency, tissue exposure & durability in CNS
- ✓ Preclinical pharmacological profile available in multiple species to inform clinical starting dose

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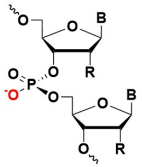
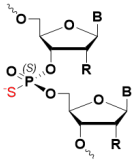
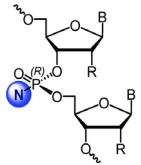
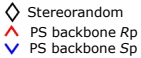
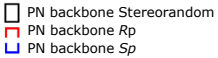
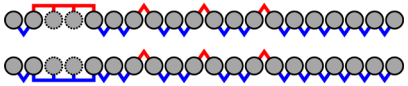
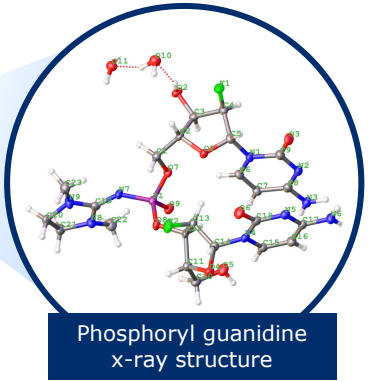
CNS, central nervous system; HTT, huntingtin

WVE-003 contains backbone modifications with novel PN backbone chemistry

Backbone linkages

	PO	PS	PN
Backbone modification (X)	Phosphodiester 	Phosphorothioate 	Phosphoramidate diester 
Stereochemistry	Not chiral	Chiral 	Chiral 
Charge	Negative	Negative	**Neutral**
Depiction			
PRISM backbone modifications	PO/PS		
	PO/PS/PN		

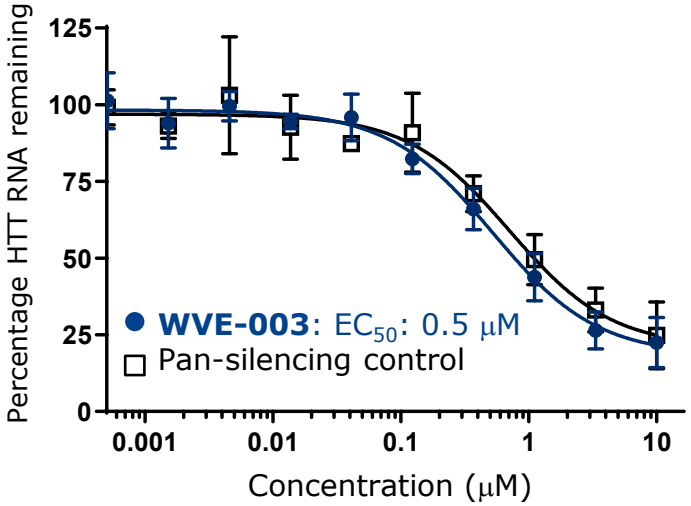


Phosphoryl guanidine x-ray structure

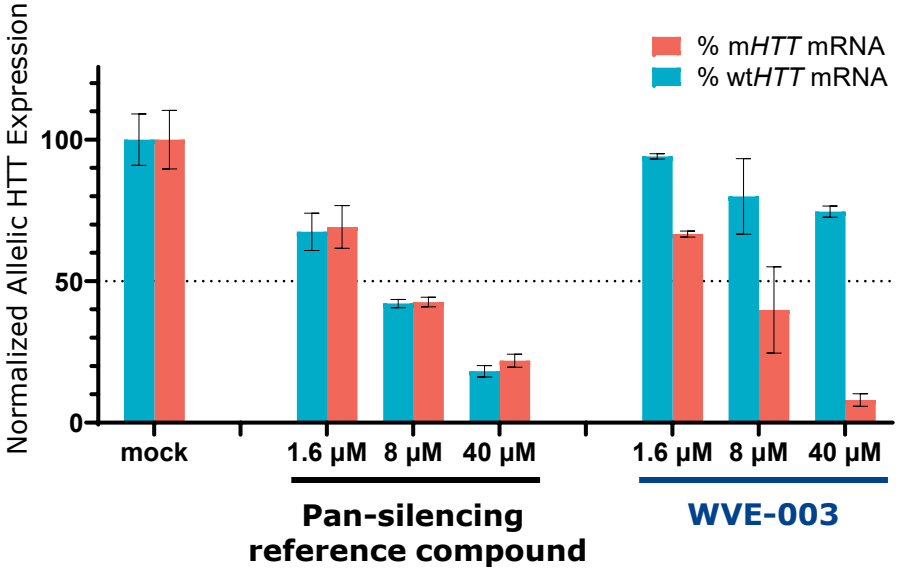
Molecule structure illustrative of backbone modification patterns

WVE-003 is potent and allele selective *in vitro*

Potently decreases HTT in HD motor neurons



Selectively reduces mHTT in HD motor neurons



Left: dose-response for HTT remaining in iPSC-derived motor neurons homozygous for SNP3, mean ± SD, n=4. Right: mHTT and wtHTT RNA expression in iPSC-derived motor neurons heterozygous for SNP3, total HTT knockdown quantified by qPCR and normalized to HPRT1 and mock treated sample. mean ± sem, n=4. iPSCs (induced pluripotent stem cells) generated from HD patient cells
mHTT, mutant HTT; wtHTT, wild-type HTT

HD mouse models

Evaluation of potency

BACHD Mouse[1]

HTT	Key characteristics
mHTT (human)	❖ 97 CAA-CAG repeats ❖ Multiple copies ❖ Subset of copies contain SNP3
wtHTT (mouse)	❖ Mouse genomic *Hdh* ❖ Lacks SNP3

Evaluation of selectivity

Hu97/18 Mouse[2]

HTT	Key characteristics
mHTT (human)	❖ 97 CAA-CAG repeats ❖ Multiple copies ❖ Subset of copies contain SNP3
wtHTT (human)	❖ 18 CAG repeats ❖ Lacks SNP3 ❖ Lacks mouse *Hdh*

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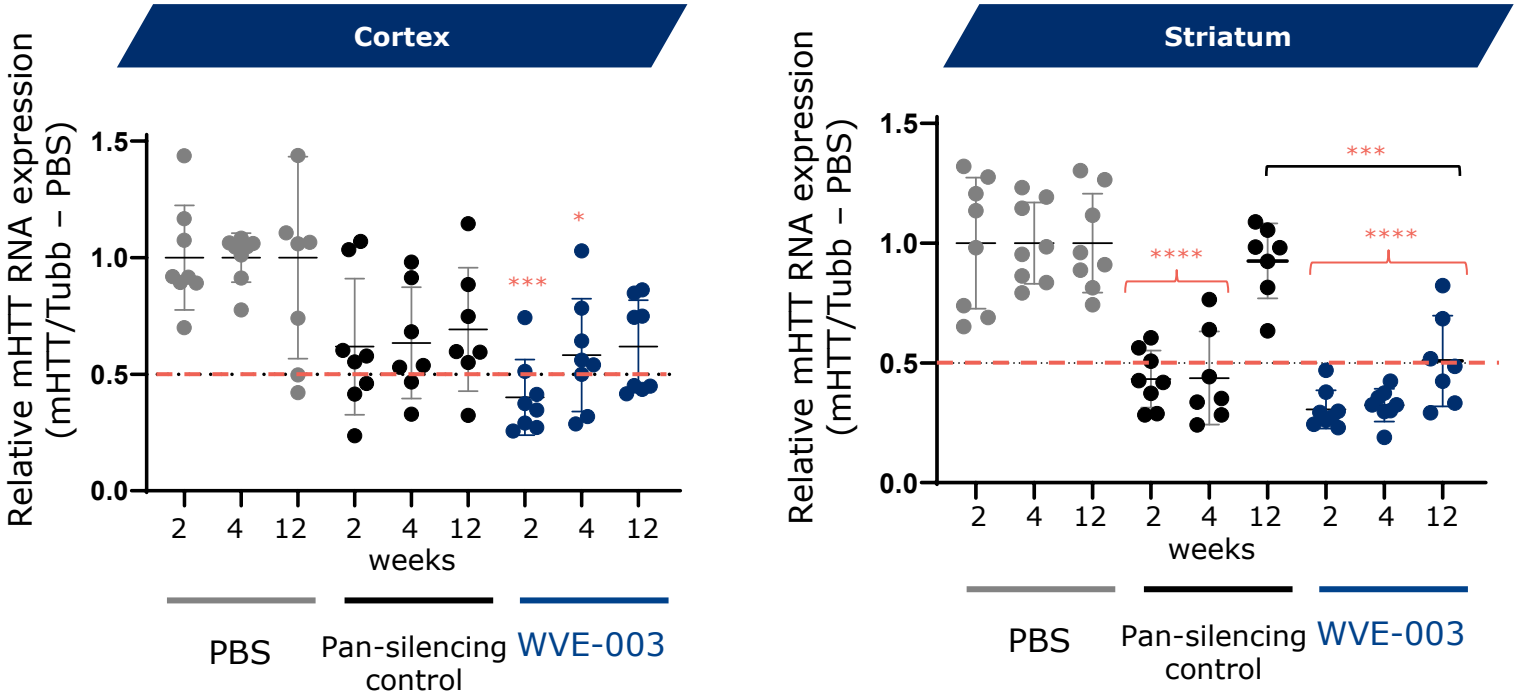
1. Gray et al., 2008 J Neurosci. 28:6182-95, 2. Southwell et al., 2013 Hum Mol Genet. 22:18-34.

WVE-003 has potent and durable effects in cortex and striatum

Maximum knockdown of 75% with ~50% knockdown persisting for at least 3 months

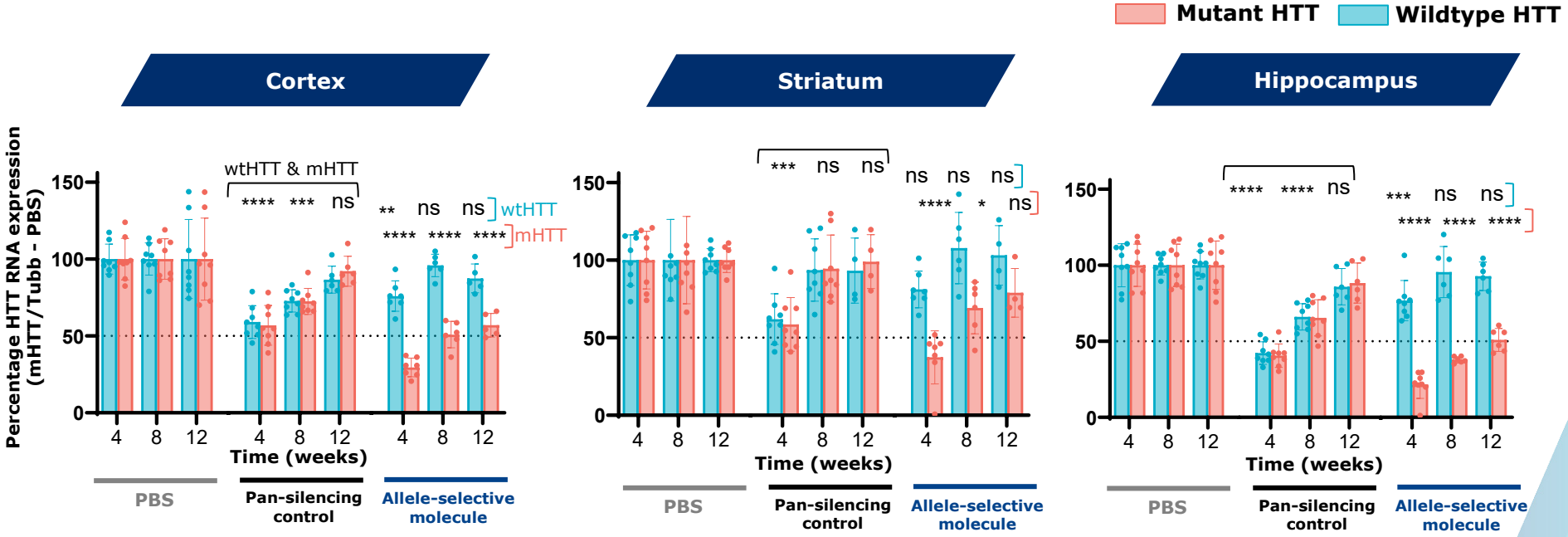


BACHD mouse

BACHD mice administered 3x100 μg intracerebroventricular doses PBS or oligonucleotide. (Left) Relative mHTT RNA in cortex at 2, 4 and 12-weeks post-dosing. (Right): Relative mHTT in striatum at same time points as cortex. BACHD contains SNP3 only in some mHTT transgenes. Data are mean ± SD, n=8. *P<0.0332, ***P<0.0002, ****P<0.0001 versus PBS unless otherwise noted). P values were calculated via 1-way analysis of variance. mHTT, mutant HTT; Tubb, tubulin

Allele-selective activity in CNS of Hu97/18 mice

*Allele-selective molecule **decreases mutant HTT, spares wildtype HTT**; whereas pan-acting molecule uniformly decreases wildtype HTT and mutant HTT*



Hu97/18 mouse

Hu97/18 mice administered 3x100 μg intracerebroventricular doses PBS or oligonucleotide. Relative mHTT RNA in cortex (left) striatum (middle) or hippocampus (right) at 4, 8 and 12-weeks post-dosing. Data are mean ± SD, n=8. Stats: ns non-significant, *P<0.05, **P<0.01, ***P<0.0001, ****P<0.0001 versus PBS by 1-way ANOVA. mHTT, mutant HTT; wtHTT, wildtype HTT; Tubb, tubulin

Preclinical pharmacological modeling available to inform clinical starting dose

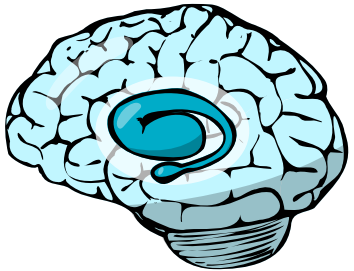
BACHD

Ascending dose studies
- PK & mHTT knockdown data
- IC_{50} determination

NHP

Concentrations in **cortex** and **striatum** sufficient for target engagement

Human
(cortex, striatum)



Anticipated mHTT knockdown in **cortex** and **striatum**

PK: pharmacokinetic PD: pharmacodynamic IC_{50}: the concentration of observed half of the maximal effect mHTT: mutant huntingtin protein

Advancing investigational WVE-003 into a Phase 1b/2a clinical trial

Leverage learnings from PRECISION-HD clinical trials

- ✓ Validated genotyping assay in CLIA setting to improve efficiency of patient identification
- ✓ Qualified biomarker assay to measure wildtype HTT protein in CSF
- ✓ Clinical experience of sites from PRECISION-HD

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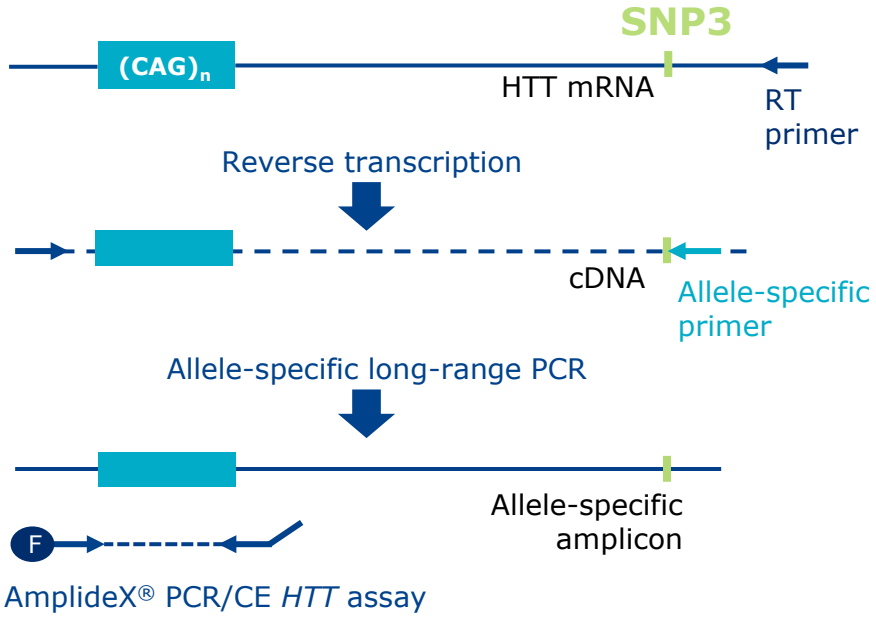
CSF, cerebrospinal fluid; mHTT, mutant huntingtin; wtHTT, wildtype huntingtin

Rapid patient identification

Investigational assay enables SNP genotyping and phasing with CAG-repeat expansion



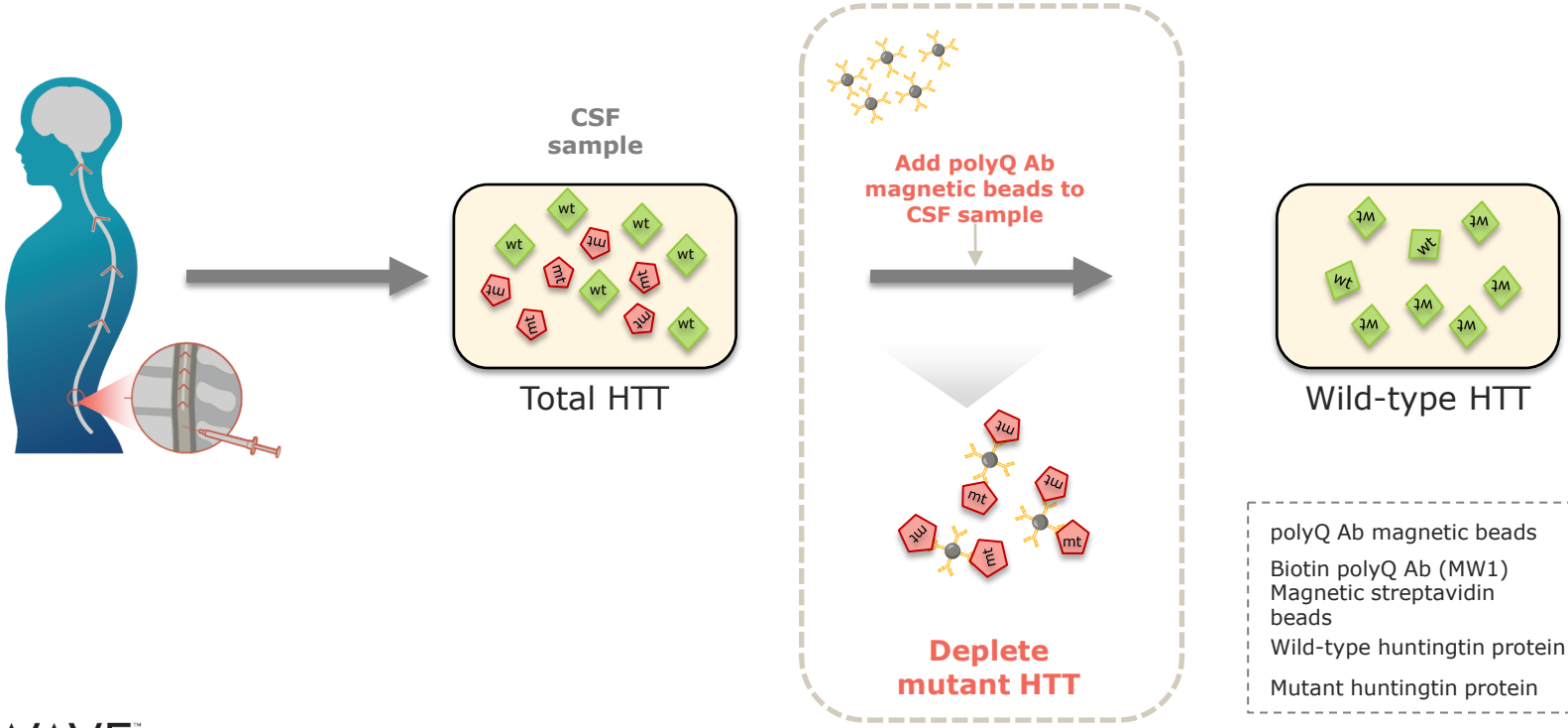
AmplideX® PCR/CE *HTT* assay

- CAG length, SNP zygosity and phasing information from a single assay
- PCR-based assay using *in vitro* diagnostic device ready capillary electrophoresis (CE) platform
- CLIA validated
- 1-2 weeks turn around time

SNP single nucleotide polymorphism; PCR polymerase chain reaction; CLIA Clinical Laboratory Improvement Amendments
Cartoon adapted from poster presented at AMP 2020 by Sarah Statt (Asuragen)

Assessment of wild-type HTT protein in CSF

Immunodepletion of mHTT to measure wtHTT protein

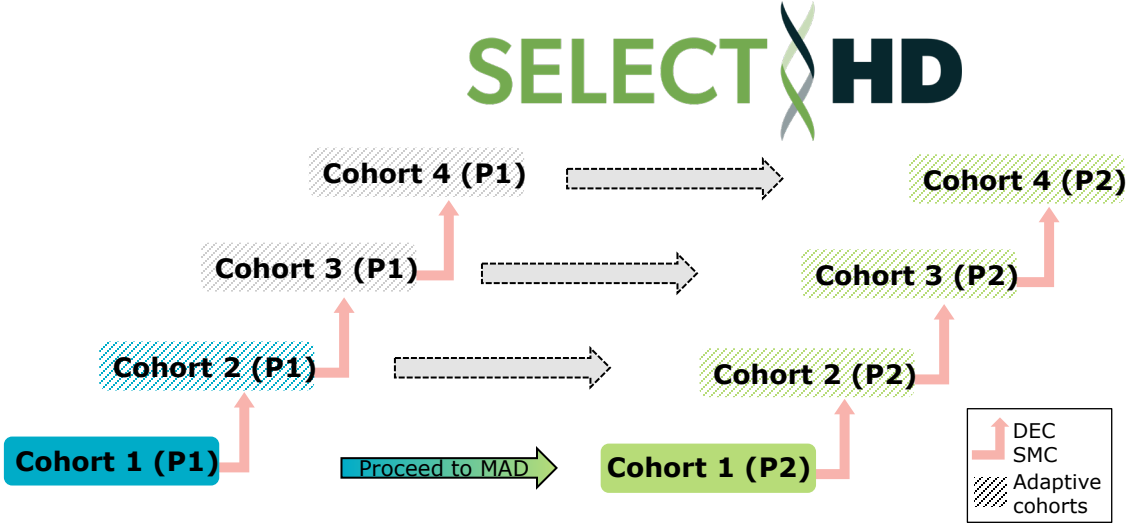


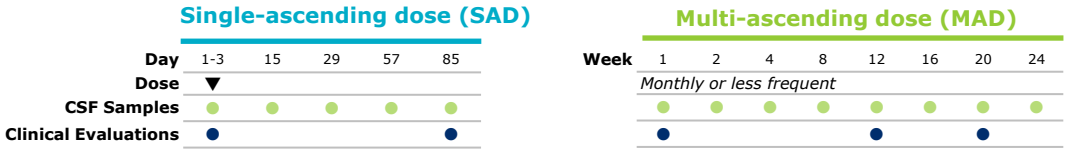
Ab, antibody; CSF, cerebrospinal fluid; mHTT, mutant HTT protein; wtHTT wild-type HTT; polyQ, poly glutamine; MW1: Wild et al., J Clin Invest, 2015.

SELECT-HD: Adaptive first-in-human study for WVE-003

Ph 1b/2a global, multicenter, randomized, double-blind placebo-controlled trial

Eligible PRECISION-HD participants can transition to this study after wash out





Patients

- Targeting 36 patients
- ≥25 and ≤60 years of age
- Confirmed early manifest HD diagnosis with SNP3 variant

Primary Objectives

- Safety and Tolerability

Secondary Objectives

- Plasma PK profile
- CSF exposure

Exploratory Objectives

Biomarkers

- mHTT
- NfL
- wtHTT
- MRI

Clinical Endpoints

- UHDRS

Adaptive cohorts: dose escalation and dosing interval guided by independent safety monitoring committee.
wtHTT, wild-type HTT; mHTT, mutant HTT; Nfl, neurofilament light chain; SNP, single nucleotide polymorphism; UHDRS, United Huntington's Disease Rating Scale; MRI, Magnetic Resonance Imaging; PK, pharmacokinetic; PD pharmacodynamic; CSF, cerebrospinal fluid; SNP, single nucleotide polymorphism; DEC, Dose Escalation Committee; SMC, Safety Monitoring Committee

Wave remains committed to an allele-selective approach in HD

SELECT HD

- **Advancing WVE-003 into SELECT-HD, a Phase 1b/2a clinical trial**
  - New chemistry has potential to address limitations of first-generation molecules in PRECISION-HD
  - Preclinical pharmacological profile available in multiple species *in vivo*
  - Initiate at pharmacologically active dose
  - Incorporates learnings from PRECISION-HD trials
  - Sites being activated, first patient has been dosed (Sept 2021)

mHTT, mutant HTT; UHDRS, United Huntington's Disease Rating Scale; MRI, Magnetic Resonance Imaging; CSF, cerebrospinal fluid; WBC, white blood cell

Acknowledgements

On behalf of Wave, thank you to all the patients, families, advocacy organizations, healthcare providers, and regulators with whom we have collaborated, particularly the study participants and families in PRECISION-HD and SELECT-HD

- **SELECT-HD Investigators**
- **SELECT-HD Clinical Advisory Committee**
  - Daniel Claassen
  - Mary Edmondson
  - Ray Dorsey
  - Ralf Reilmann
- **CHDI**
- **Asuragen**
- **EVOTEC**
- **IRBM**
- **Wave's scientists and Study Team**

For additional information on SELECT-HD contact clinicaltrials@wavelifesci.com or visit clinicaltrials.gov (NCT05032196)

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