SELECT-HD: A Ph1b/2a study of WVE-003, an investigational allele-selective, mHTT–lowering oligonucleotide for the treatment of Huntington's disease

Danlin Xu, MBBS, PhD
Medical Director, Clinical Development

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WAVE™
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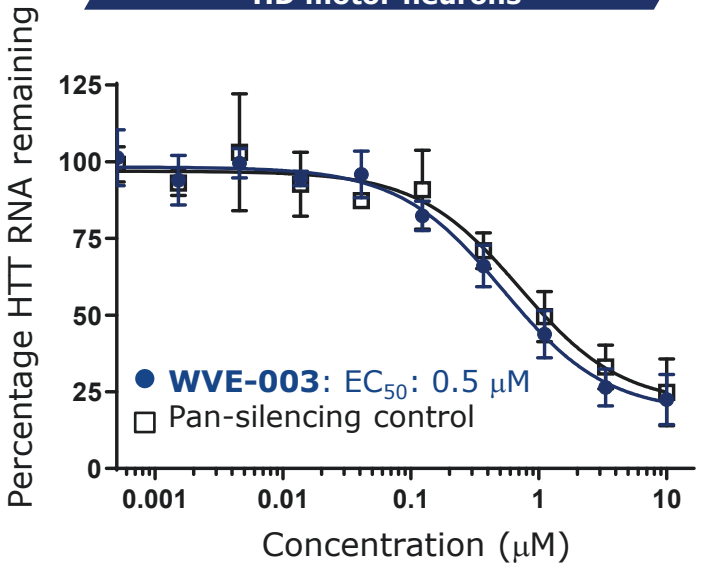
WVE-003: an investigational oligonucleotide for the treatment of early manifest Huntington's disease

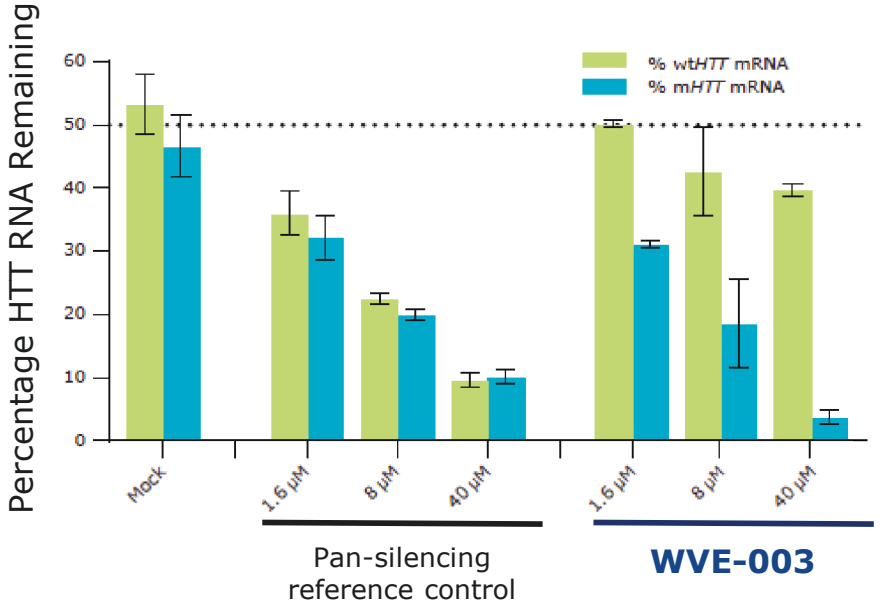
- WVE-003 is a stereopure antisense oligonucleotide
- An allele-selective molecule that decreases expression of mHTT while preserving the expression of wild type HTT by targeting at SNP3, which is only on the mHTT allele
- WVE-003 contains Wave's novel PN backbone chemistry which improves the pharmacology of oligonucleotides in preclinical studies

WVE-003 is potent and selective *in vitro*

Potently decreases HTT in HD motor neurons



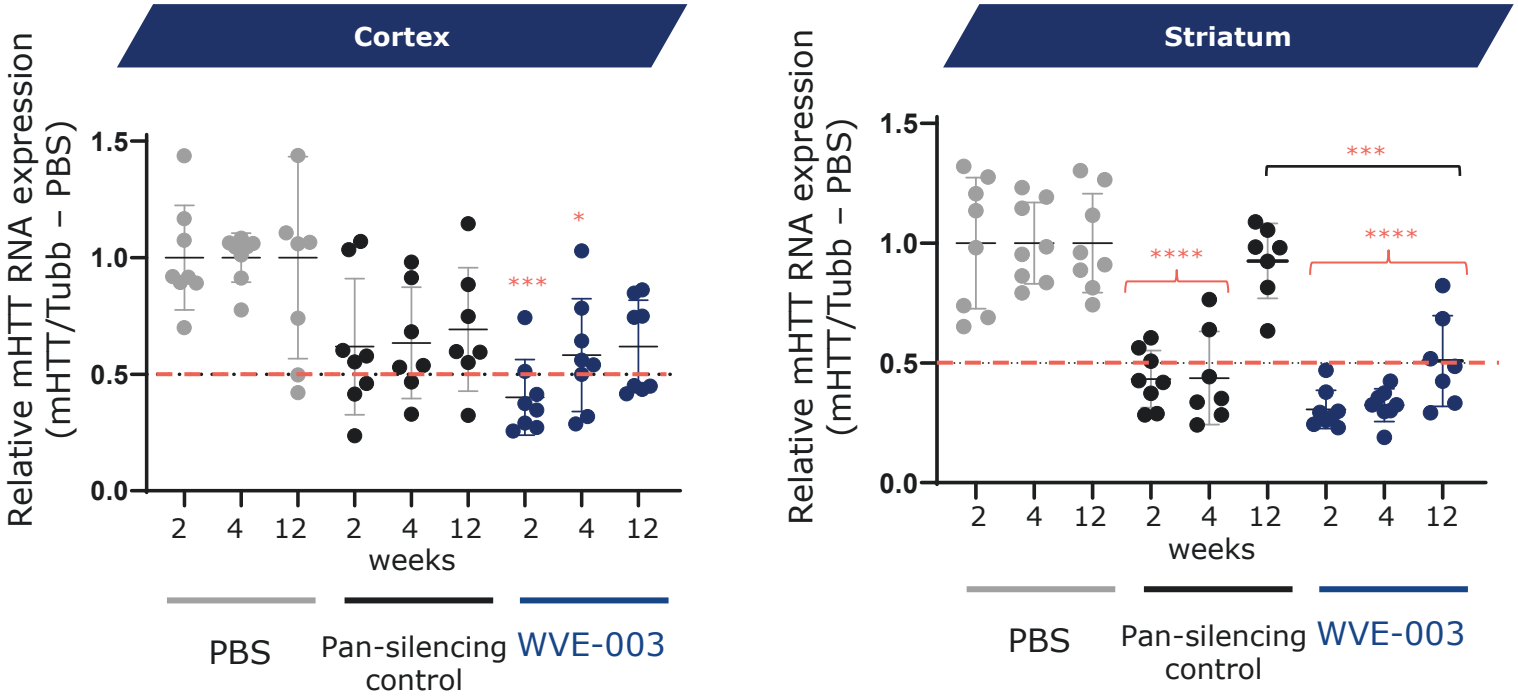
Selectively reduces mHTT in HD motor neurons



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, mean ± sem, n=4
iPSCs (induced pluripotent stem cells) generated from HD patient cells
mHTT, mutant HTT; wtHTT, wild-type HTT

WVE-003 has potent and durable effects in cortex and striatum of BACHD mice

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



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

SELECT-HD: a Ph1b/2a, multicenter, randomized, double-blind, placebo-controlled trial in patients with HD

SELECT HD

Patients

- Targeting 36 patients
- ≥18 and ≤60 years of age
- Confirmed early manifest HD diagnosis with SNP3 variant
- Eligible PRECISION-HD participants can transition to this study after wash out

Primary objective

Safety and tolerability

Secondary objectives

- WVE-003 Plasma PK profile
- WVE-003 CSF exposure

Exploratory

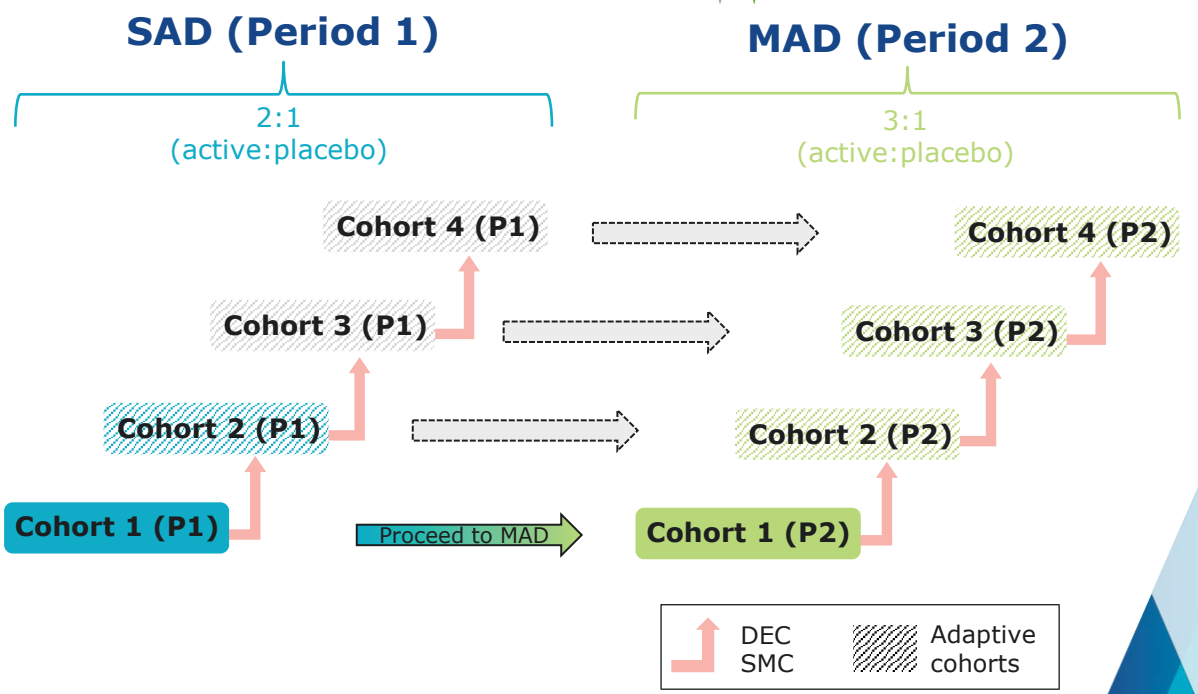
- Biomarkers: mHTT, wtHTT, NfL
- Clinical effects: UHDRS, MRI

mHTT, mutant HTT; wtHTT, wild-type HTT; NfL, Neurofilament light chain; CSF cerebrospinal fluid; PK, pharmacokinetic; UHDRS, Unified Huntington's Disease Rating Scale; MRI, Magnetic Resonance Imaging

SELECT-HD: Clinical trial to leverage experience and learnings in HD

Leveraging learnings from PRECISION HD

- Starting dose informed by preclinical *in vivo* models
- Genotyping assay to improve efficiency of patient identification
- Drawing from experience of sites from PRECISION-HD1 and PRECISION-HD2 trials



SELECT-HD

SAD, single-ascending dose; MAD, multiple-ascending dose; DEC, Dose Escalation Committee; SMC, Safety Monitoring Committee; P, period