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LIFE SCIENCES

A Ph1b/2a study of WVE-003, an investigational allele-selective, mHTT-lowering oligonucleotide for the treatment of early manifest Huntington's disease, and review of PRECISION-HD results

Vissia Viglietta, MD PhD
VP Clinical Development

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mHTT results from PRECISION-HD trials do not support further development of WVE-120102 or WVE-120101

- **PRECISION-HD2: Core Study**
 - No statistically significant reductions of mHTT after single or multiple doses of WVE-120102 (doses 2-32 mg)
 - No dose response
- **PRECISION-HD2: Open Label Extension (OLE)**
 - Modest and inconsistent reductions in mHTT over course of study
 - Additional dose escalation unlikely to achieve drug concentrations needed for robust mHTT knockdown
 - No correlation between >20% mHTT reduction and wtHTT change, suggesting allele selectivity
- **PRECISION-HD1: Core and OLE**
 - Results consistent with PRECISION-HD2 up to 16 mg; 32 mg core and OLE results pending
- **Additional observations from all studies**
 - No changes in NfL over time
 - No worsening of disease progression in treated participants versus expected based on natural history
 - Biomarker assays (mHTT, wtHTT, and NfL) performed reliably

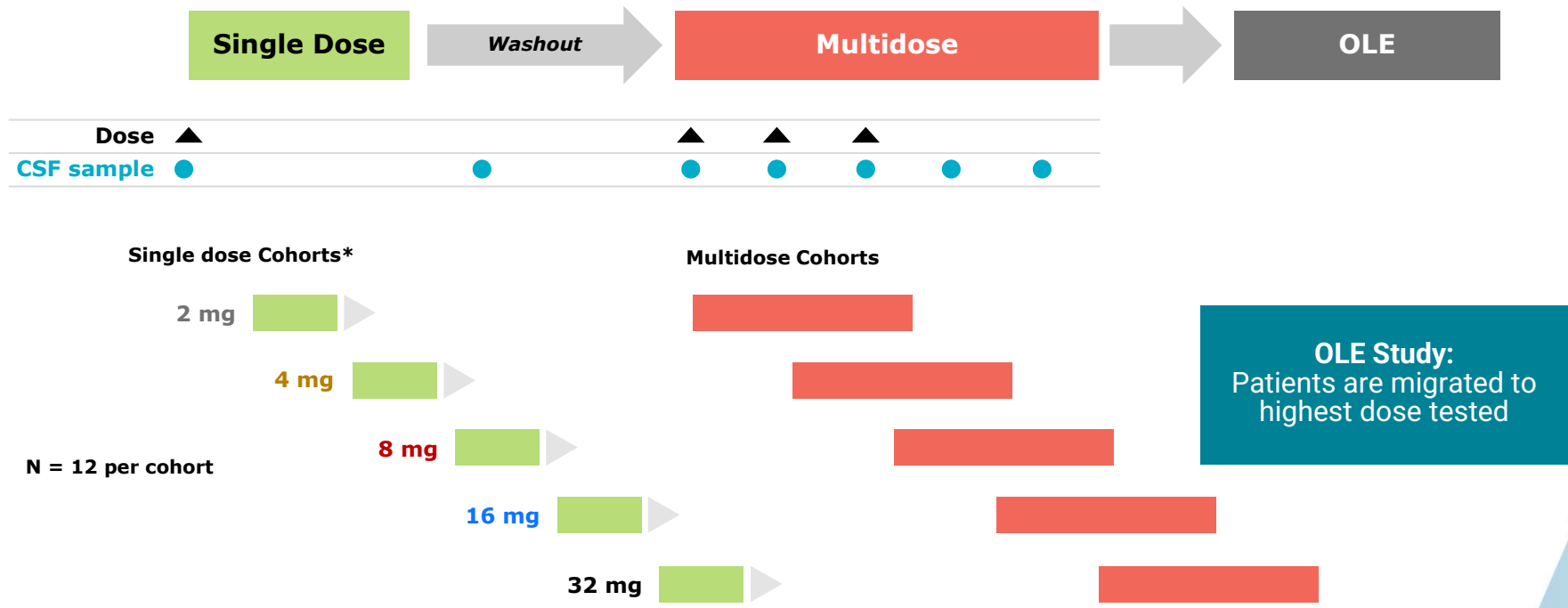
PRECISION-HD2

PRECISION-HD1

WVE-003

mHTT, mutant HTT; wtHTT wild-type HTT; NfL neurofilament light chain

PRECISION-HD study design



PRECISION-HD2
 PRECISION-HD1
 WVE-003

OLE: Open label extension; CSF: cerebrospinal fluid; mHTT: mutant huntingtin; *12 mg single-dose cohort in PRECISION-HD2, US only



PRECISION-HD2: Patient Disposition

WVE-120102

	Placebo (pooled)	2 mg	4 mg	8 mg	12 mg	16 mg	32 mg	Total
Number of patients	22	9	12	15	8	9	13	88
No. of doses per patient								
1	6	3	4	7	8	0	6	28
2	0	0	0	0	0	0	0	0
3	3	0	3	6	0	0	3	12
4	13	6	5	2	0	9	4	26
Mean	3.0	3.0	2.8	2.2	1.0	4.0	2.4	2.5
Patients who prematurely discontinued treatment	0	2 (22.2)	1 (8.3)	0	0	0	7 (53.8)	10 (11.4)
AEs	0	0	0	0	0	0	6 (46.2)	6 (6.8)

PRECISION-HD2

PRECISION-HD1

WVE-003

No., number; AEs, adverse events
Numbers in parenthesis are percentages

PRECISION-HD2: Patient Demographics and HD Disease History

WVE-120102

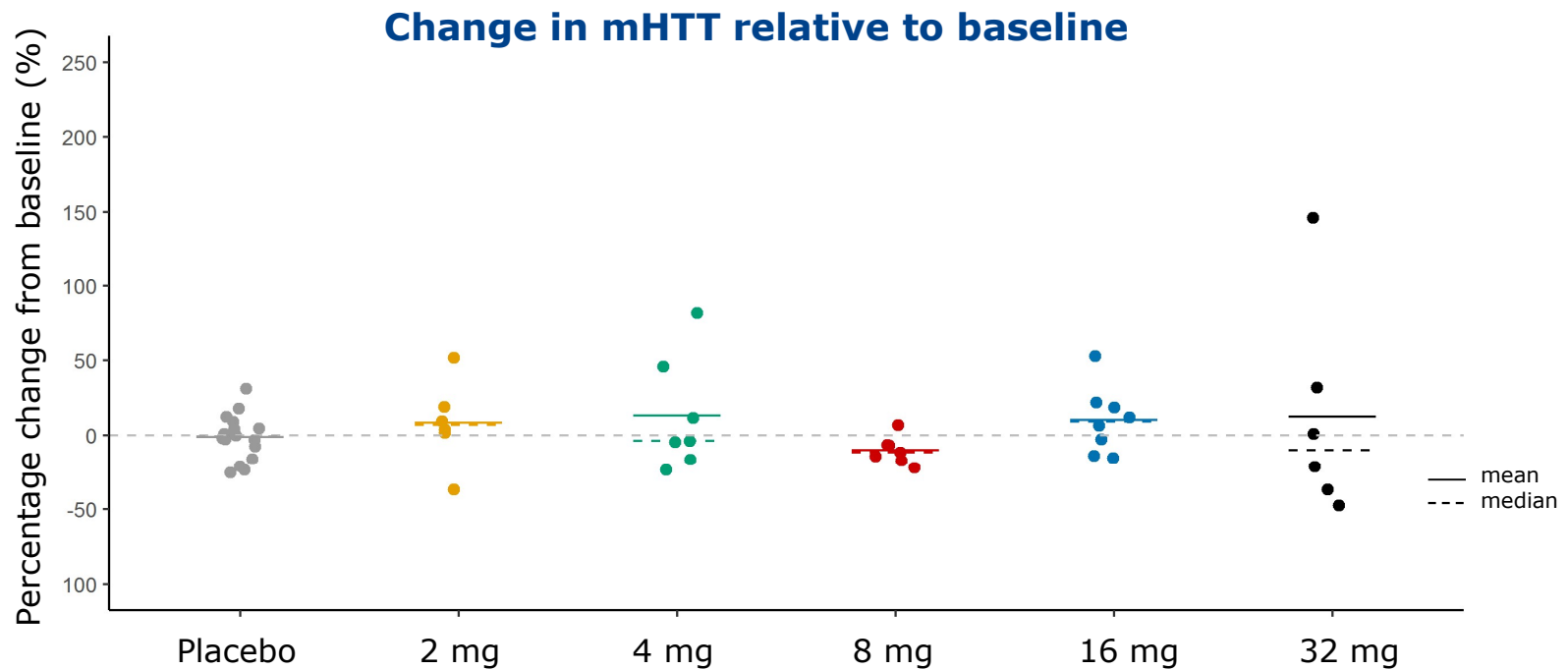
	Placebo (pooled) (n=22)	2 mg (n=9)	4 mg (n=12)	8 mg (n=15)	12 mg (n=8)	16 mg (n=9)	32 mg (n=13)	Total (active) (n=66)
Mean time since initial diagnosis (y)	6.1	9.9	3.8	5.6	3.9	3.2	5.6	5.3
Mean age at HD onset (y)	40.18	42	41.75	43.33	42.50	49	48.08	44.47
Diagnosis Stage								
1	9 (40.9)	5 (55.6)	6 (50)	8 (53.3)	1 (12.5)	5 (55.6)	11 (84.6)	36 (54.5)
2	13 (59.1)	4 (44.4)	6 (50)	7 (46.7)	7 (87.5)	4 (44.4)	2 (15.4)	30 (45.5)
Mean CAG repeat length	45	44.22	44	43.73	45.13	43.44	42.62	43.76
Mean CAP score	502.36	533.72	459.89	475.51	519.65	504.84	473.92	489.64

- PRECISION-HD2
- PRECISION-HD1
- WVE-003

Y, years; HD Huntington’s disease
Numbers in parenthesis are percentages



PRECISION-HD2 core: No statistically significant reduction of mHTT detected after 3 or 4 doses of WVE-120102

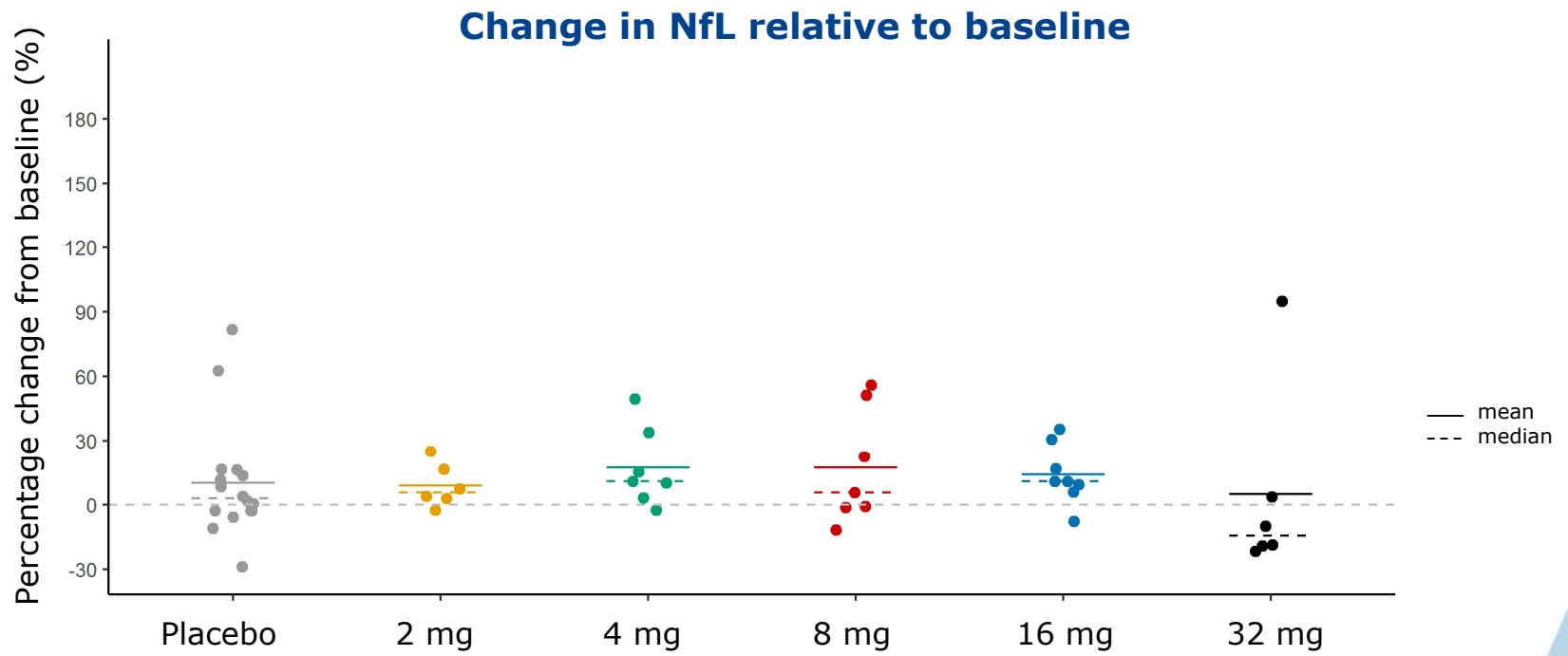


- PRECISION-HD2
- PRECISION-HD1
- WVE-003

mHTT, mutant HTT



PRECISION-HD2 core: No statistically significant changes in NfL detected after 3 or 4 doses of WVE-120102



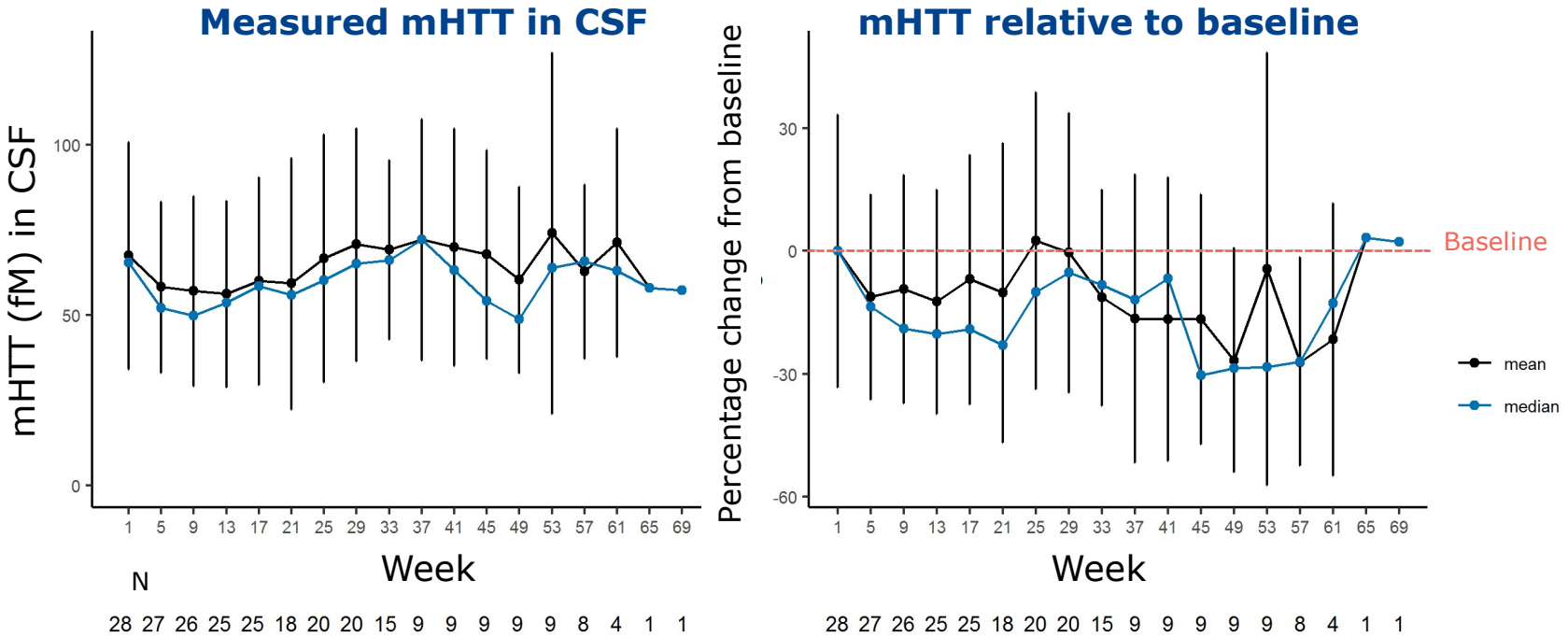
- PRECISION-HD2
- PRECISION-HD1
- WVE-003

NfL, neurofilament light chain



PRECISION-HD2 OLE: Modest reductions of mHTT at some timepoints

Multiple prespecified and ad hoc sensitivity analyses confirmed no consistent effects



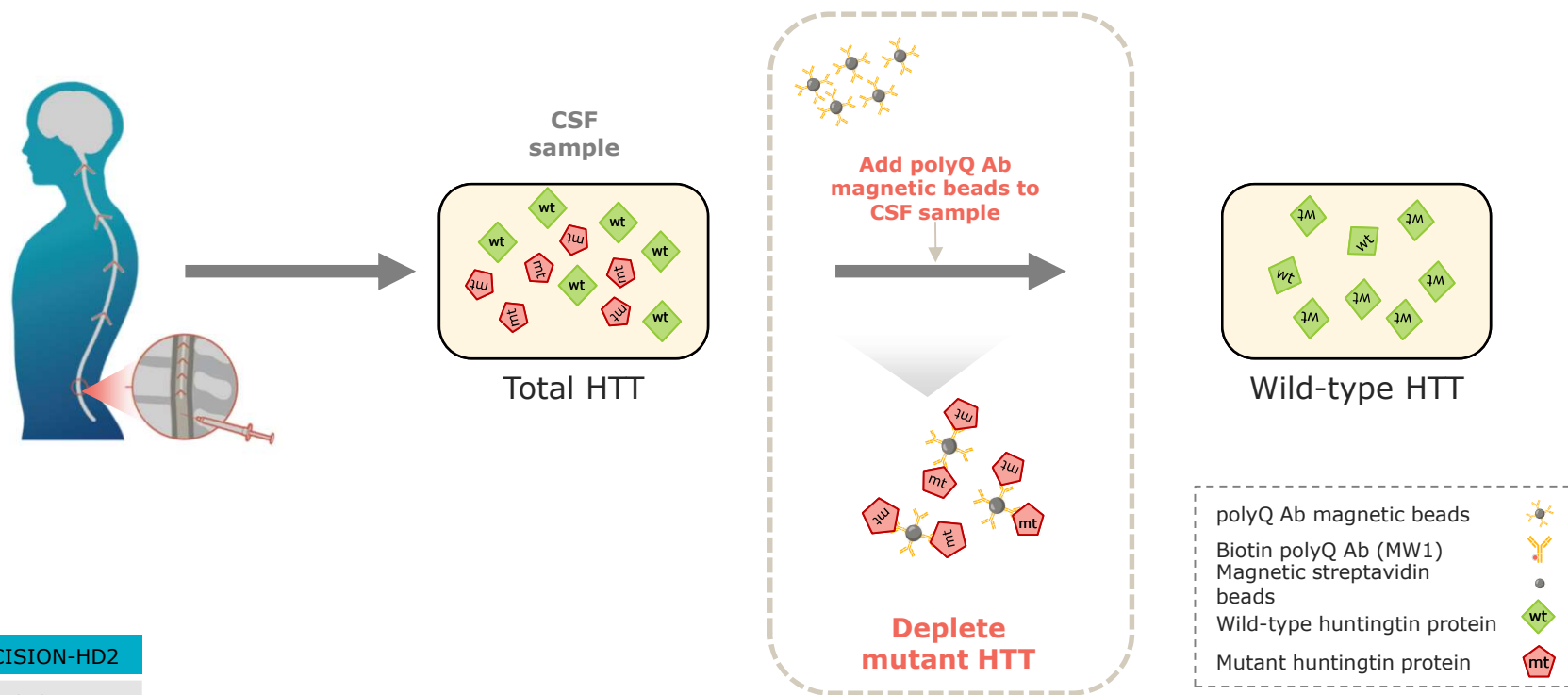
PRECISION-HD2
PRECISION-HD1
WVE-003

In PRECISION-HD2 OLE, 36 patients were receiving active treatment and were included in the safety assessment. They had received a mean of 9.3 monthly doses (Range: 1-19 doses). 28 patients were included in the biomarker analysis, having received a mean of 8.1 monthly doses (Range: 1-17 doses). Data are represented as mean ± SD and median, mHTT, mutant HTT; CSF, cerebrospinal fluid; OLE, open label extension



Assessment of wild-type HTT protein in CSF

Immunodepletion of mHTT to measure wtHTT protein



PRECISION-HD2

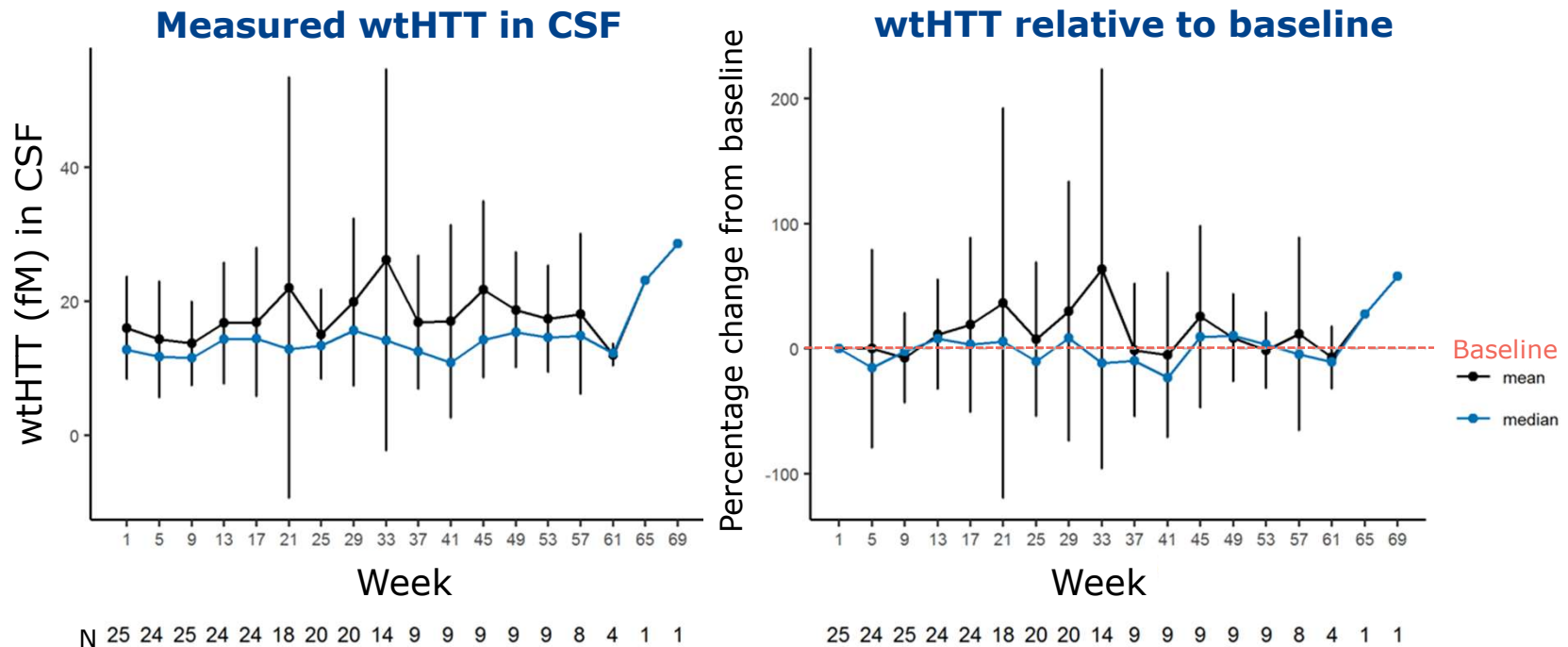
PRECISION-HD1

WVE-003

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

PRECISION-HD2 OLE: No reductions in wtHTT over time

No correlation between greater than 20% reduction in mHTT and wtHTT change suggests allele-selectivity (correlation coefficient = 0.4, 95% CI: -0.22-0.19)

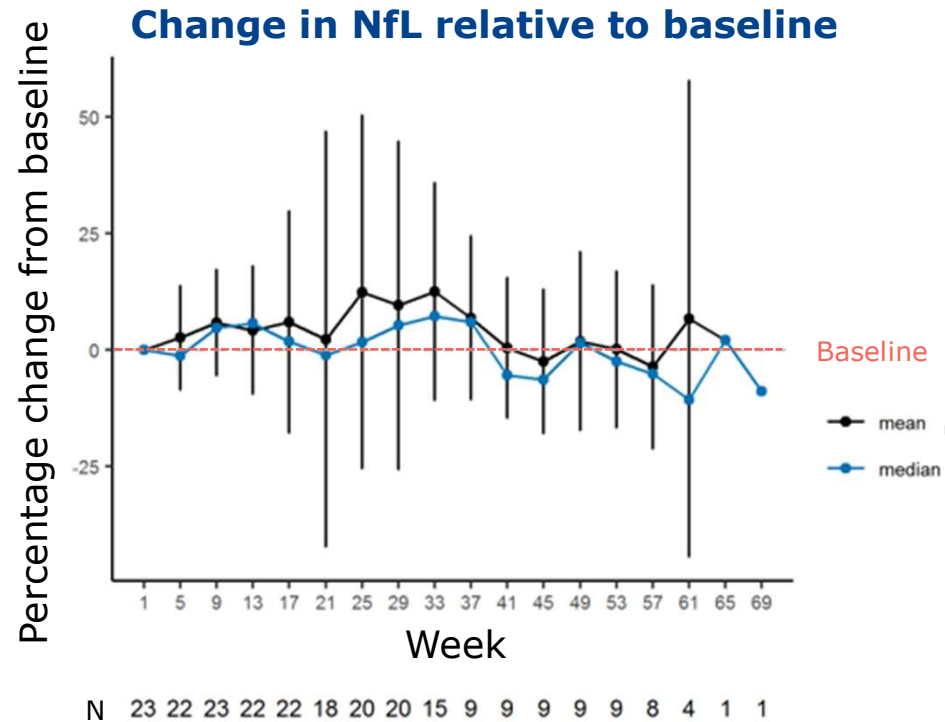


PRECISION-HD2
 PRECISION-HD1
 WVE-003

Data are represented as mean ± SD and median. Lack of robust reduction in mHTT limits ability to be definitive. mHTT, mutant HTT; wtHTT, wild-type HTT; CSF cerebrospinal fluid; OLE, open label extension



PRECISION-HD2 OLE: No changes in NfL over time



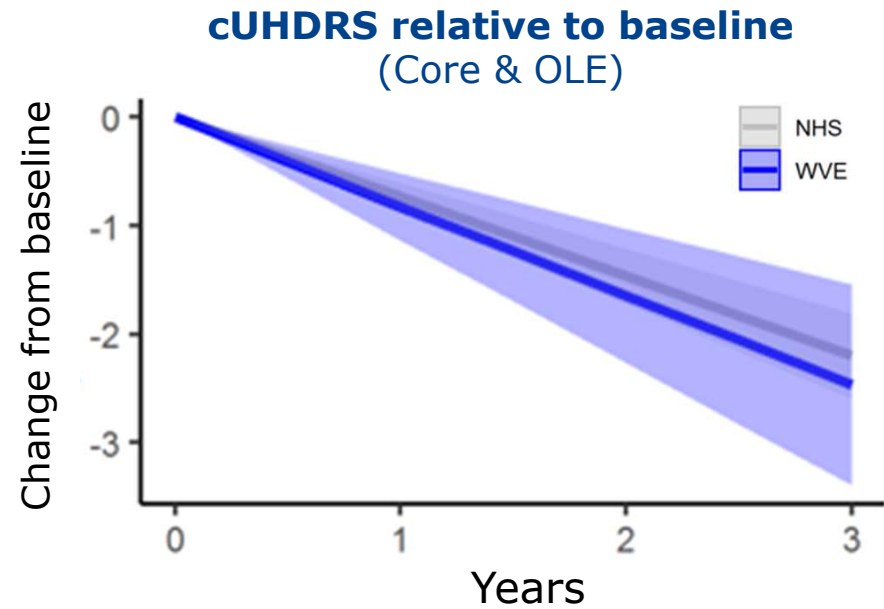
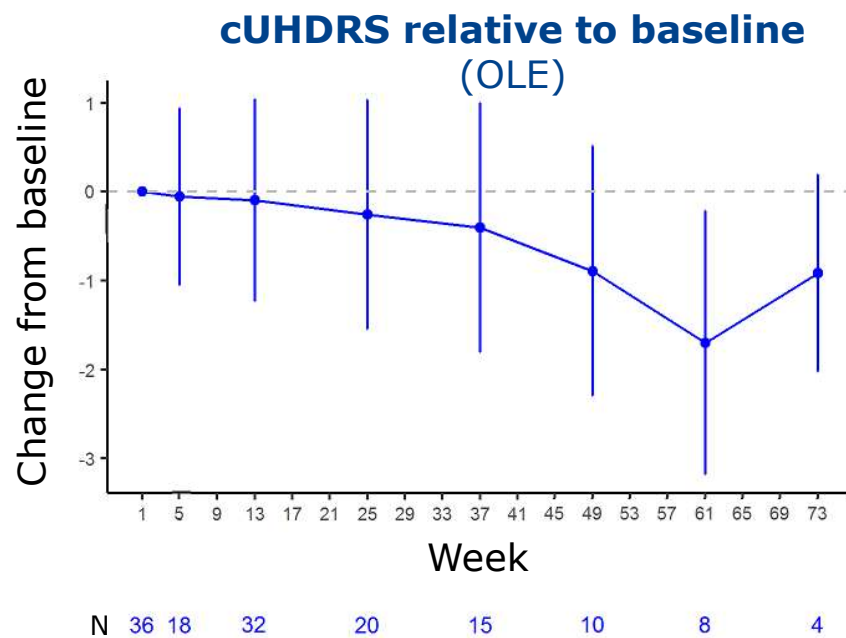
PRECISION-HD2

PRECISION-HD1

WVE-003

NfL, neurofilament light chain; OLE, open label extension
Data are represented as mean \pm SD and median

Progression on UHDRS-based endpoints matched that expected from natural history studies (NHS)



- PRECISION-HD2
- PRECISION-HD1
- WVE-003

CHDI provided data from Track-HD, Predict-HD, Enroll-HD for natural history studies
 UHDRS, Unified Huntington's disease rating scale; cUHDRS, composite UHDRS; OLE, open-label extension



PRECISION-HD2 Core and OLE Safety

Core

- AEs reported in 83% of WVE-120102-treated participants versus 90% on placebo, most mild to moderate in intensity
 - Most common (reported in $\geq 10\%$ receiving WVE-120102): Headache, procedural pain, back pain, falls, viral upper respiratory tract infection, dizziness, and post-lumbar puncture syndrome
 - SAEs increased in the 32 mg group as compared to lower doses
 - 7 of 13 patients were reported with an SAE related to treatment
 - 6 discontinued treatment due to AE
 - SAEs were transient and included disorientation, delirium, ataxia, slurred speech, amnesia, meningitis, fever and vertigo

OLE

- AEs were similar to core study
 - 36 patients reported with an event over 327 person/months of exposure
 - Incidence of SAEs related to treatment with 32 mg WVE-120102 was lower than in the core study
 - 3 patients discontinued treatment due to AEs (2 receiving 16 mg, 1 receiving 32 mg)

PRECISION-HD2

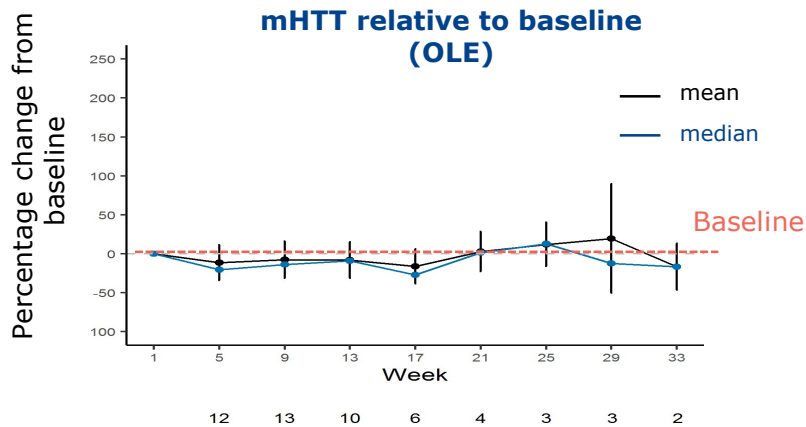
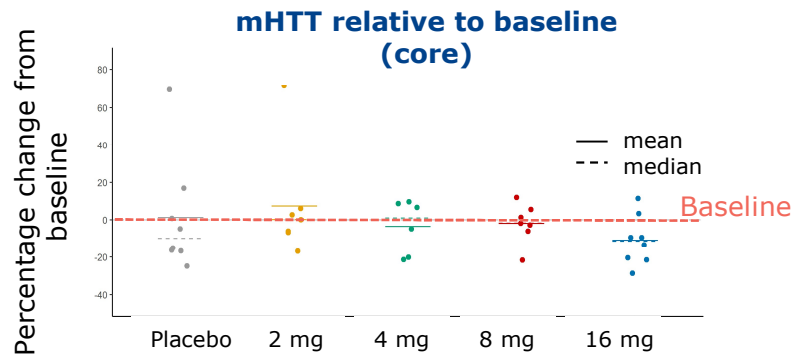
PRECISION-HD1

WVE-003

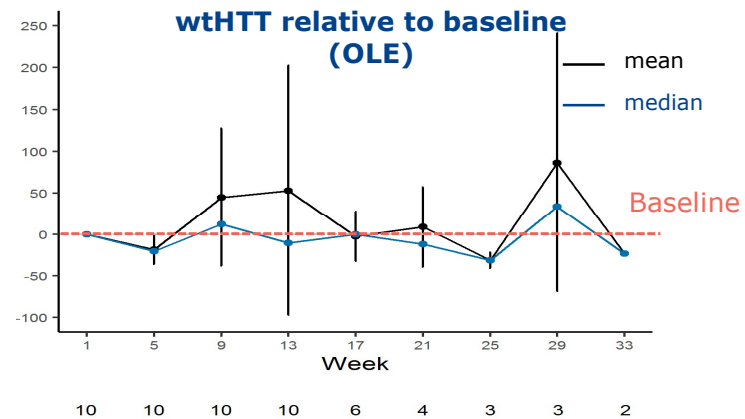
No clinically meaningful trends in clinical laboratory values, including no CSF WBC and protein elevations in either study

OLE, open-label extension; AEs, adverse events; SAEs, serious adverse events; CSF, cerebrospinal fluid; WBC, white blood cell

PRECISION-HD1: No change in mHTT in core or OLE; generally safe and well tolerated



- Patient disposition & demographics matched PRECISION-HD2 with fewer discontinuations
- No statistically significant changes in mHTT, wtHTT, or NfL in core or OLE
- AE: 91% (WVE-120101-treated) versus 75% (placebo); most were mild to moderate in intensity and were similar between core and OLE
- SAE: 1 patient with gait disturbance in OLE

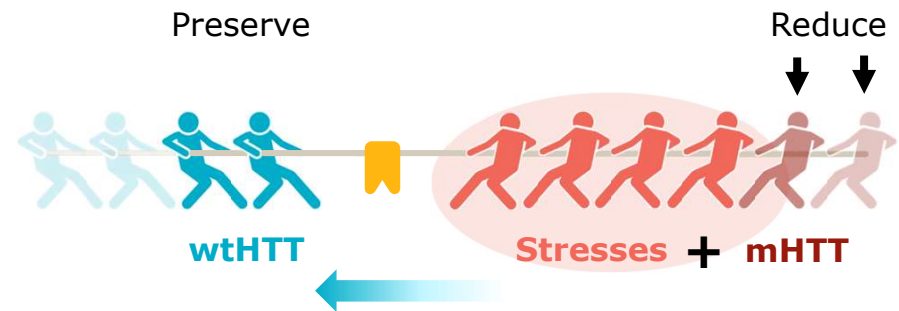
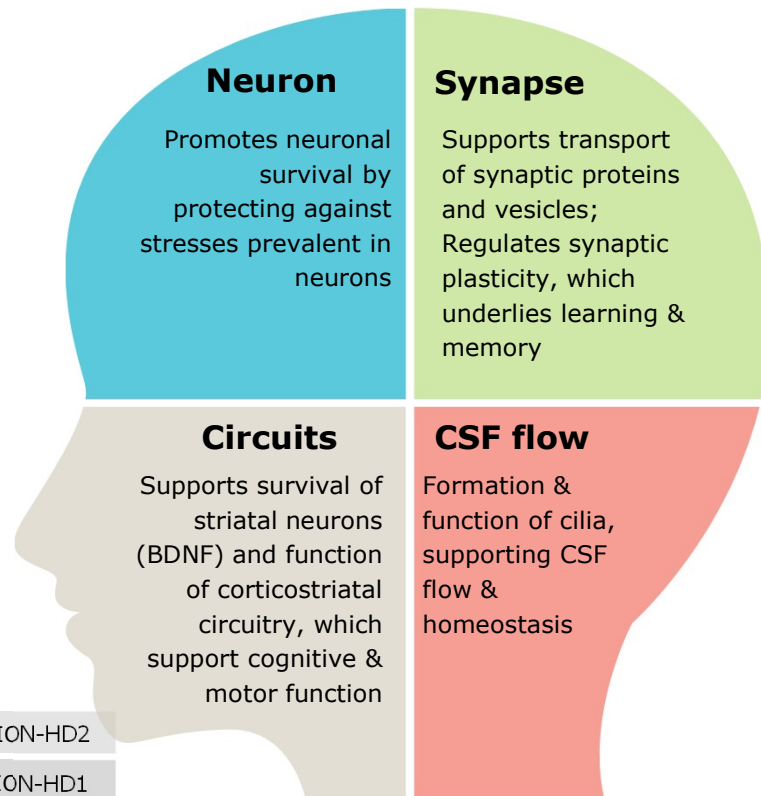


PRECISION-HD1

OLE open-label extension; mHTT mutant HTT; wtHTT wild-type HTT; NfL neurofilament light chain; AE adverse event; SAE serious adverse event

Allele-selective approach to treating HD

Reduce mHTT & preserve wtHTT, which supports brain function at multiple levels



- ✓ Target mHTT transcript to reduce mHTT protein
- ✓ Preserve protective wtHTT reservoir in brain

PRECISION-HD2

PRECISION-HD1

WVE-003

mHTT, mutant HTT; wtHTT, wild-type HTT; CSF, cerebrospinal fluid

Introducing WVE-003, an investigational oligonucleotide

WVE-003
SNP3

- ✓ **Allele-selective approach for lowering mHTT**
Designed to preserve wtHTT protein
- ✓ **Contains Wave's new chemistry**
PN chemistry has demonstrated enhanced potency, tissue exposure & durability in CNS
- ✓ **Clinical starting dose informed by preclinical *in vivo* models**
Insight into PK / PD relationships in multiple species
- ✓ **Clinical trial efficiencies**
Adaptive trial design may enable rapid POC

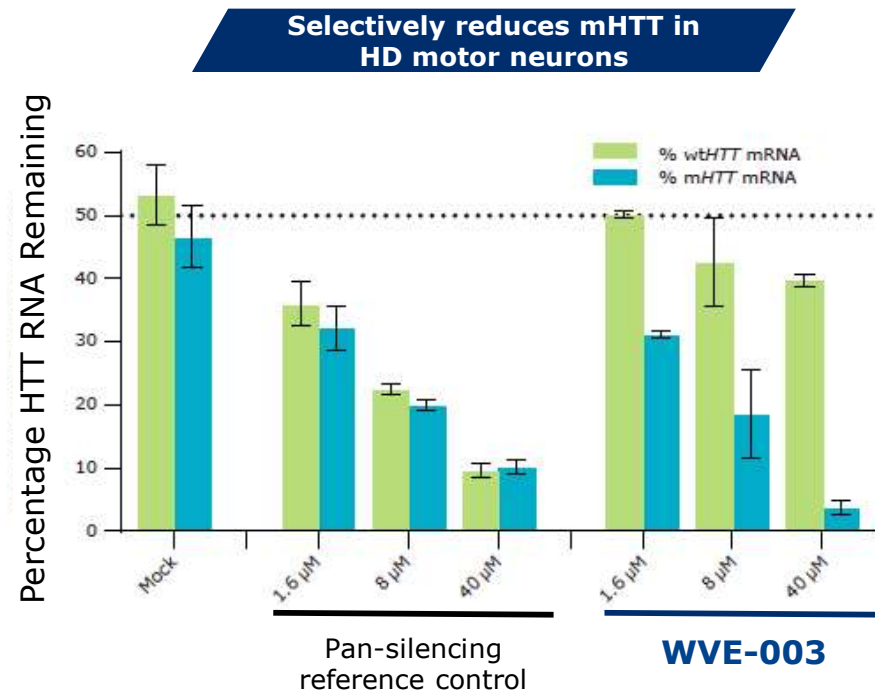
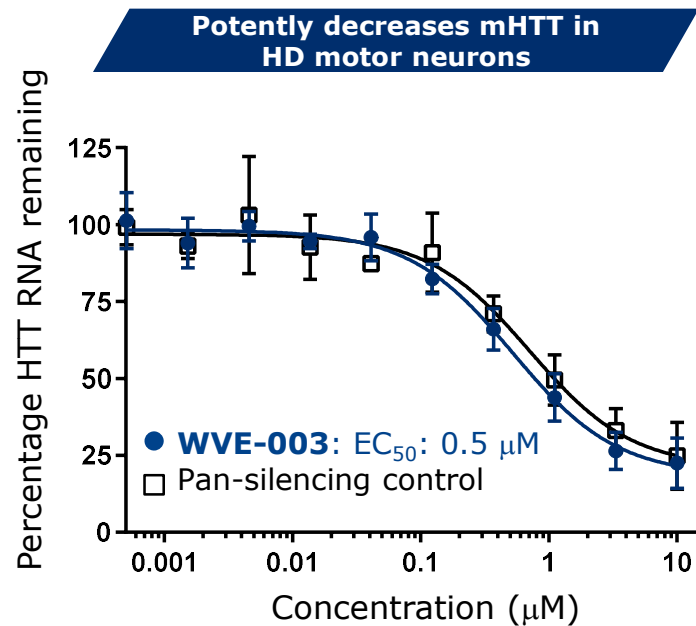
PRECISION-HD2

PRECISION-HD1

WVE-003

wtHTT, wild-type HTT; mHTT, mutant HTT; CNS central nervous system; PK, pharmacokinetic; PD pharmacodynamic; POC, proof of concept; SNP, single nucleotide polymorphism

WVE-003 is potent and selective *in vitro*



PRECISION-HD2

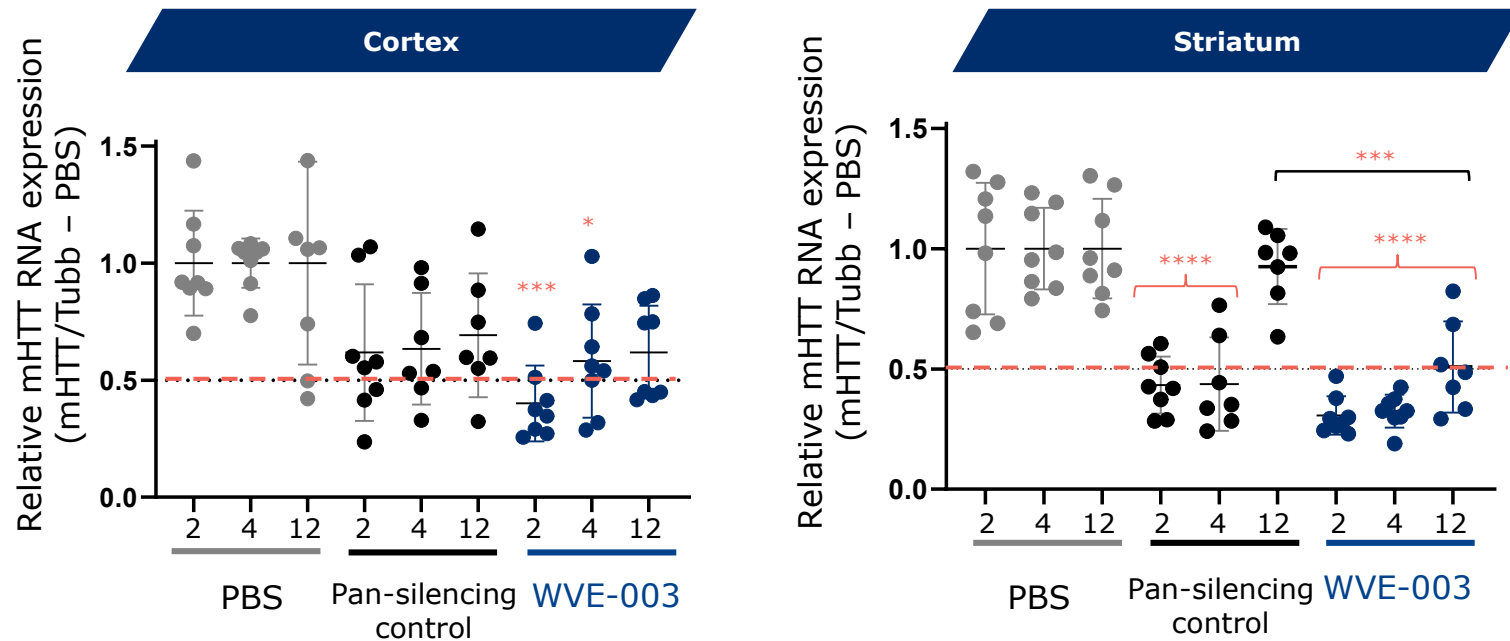
PRECISION-HD1

WVE-003

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 70-75% with ~50% knockdown persisting for at least 3 months



PRECISION-HD2

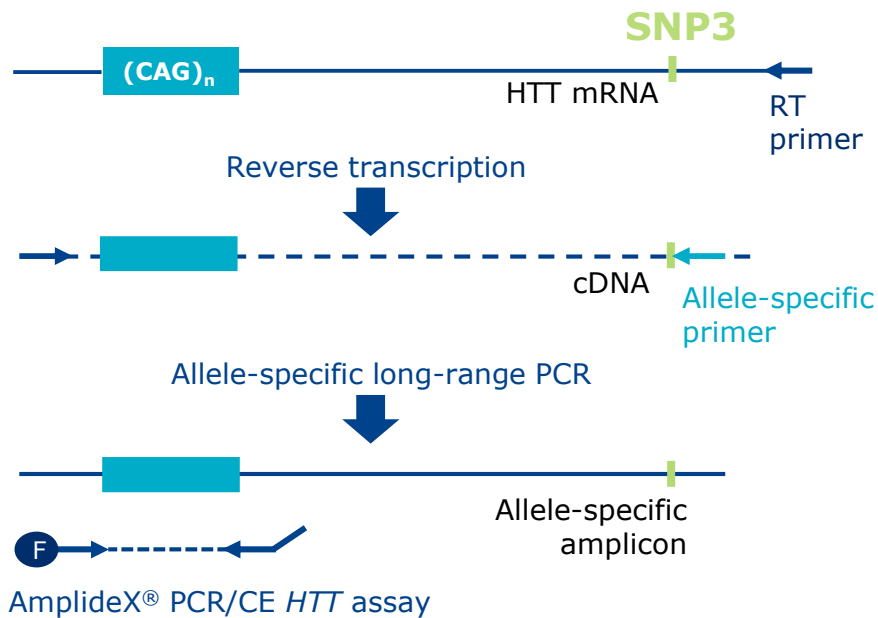
PRECISION-HD1

WVE-003

BACHD mice administered 3x100 μ g 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 in some mHTT transgenes. Data are mean \pm 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

Rapid patient identification

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

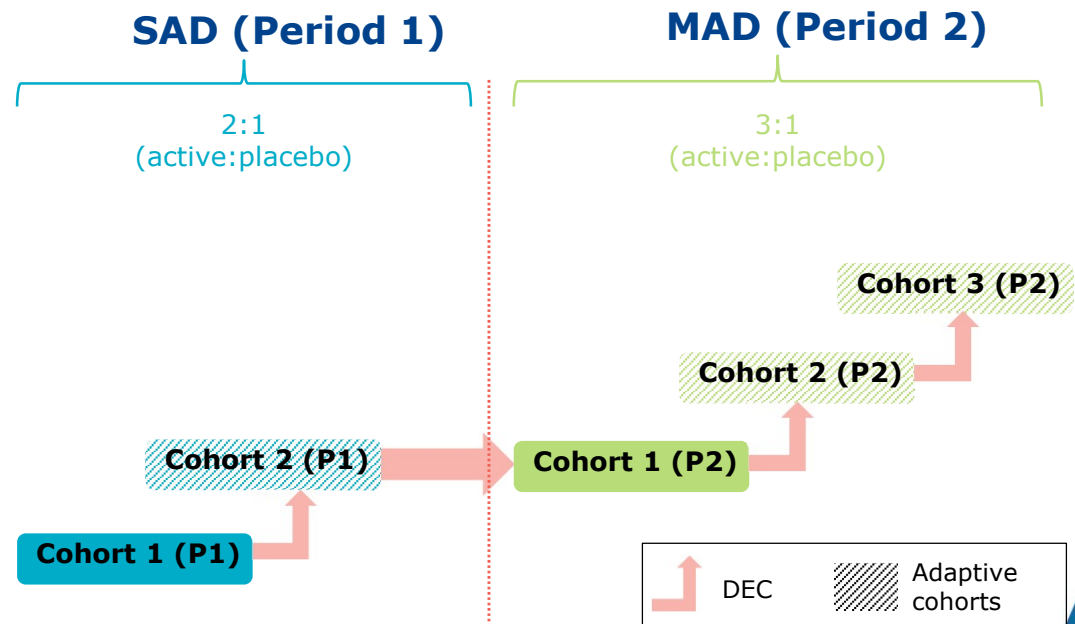


- CAG length, SNP zygosity and phasing information from a single assay
- PCR-based assay using *in vitro* diagnostic device ready capillary electrophoresis (CE) platform
- CLIA validated
- 1-2 weeks turn around time

WVE-003: 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



PRECISION-HD2

PRECISION-HD1

WVE-003

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

Adaptive SAD/MAD Ph1b/2a study for WVE-003

Multicenter, randomized, double-blind, placebo-controlled trial

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

Patients

- Targeting 36 patients
- ≥ 18 and ≤ 60 years of age at screening visit
- Confirmed manifest HD diagnosis with SNP3 variant

Primary objective

- Safety and tolerability

Secondary objectives

- Plasma PK profile
- CSF exposure

Exploratory

- Biomarkers: mHTT, wtHTT, NfL
- Clinical endpoints: UHDRS

Trial oversight and status

- Dose escalation and dosing interval guided by independent DSMB
- Site activation ongoing
- Dosing expected to initiate in 2021

PRECISION-HD2

PRECISION-HD1

WVE-003

SAD, single-ascending dose; MAD, multiple ascending dose; mHTT, mutant HTT; wtHTT, wild-type HTT; NfL, Neurofilament light chain; CSF cerebrospinal fluid; PK, pharmacokinetic; DSMB, Dose Safety Monitoring Board; P period

Wave remains committed to an allele-selective approach in HD

- **Results from PRECISION-HD trials do not support further development of WVE-120102 and WVE-120101**
- **Advancing WVE-003 into Phase 1b/2a clinical trial**
 - New chemistry has potential to address limitations of first-generation molecules
 - Preclinical pharmacological profile available in multiple species *in vivo*
 - Initiate at a dose predicted to be pharmacologically active
 - Incorporates learnings from PRECISION-HD trials
 - Adaptive study design, with potential for rapid proof of concept
 - Sites being activated, dosing expected to initiate in 2021

Acknowledgements

PRECISION-HD study participants & families

PRECISION-HD Investigators

- Robert Adam
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Clinical Advisory Committee

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

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Wave's scientists and study team

