PRECISION-HD2 Topline Results

December 30, 2019

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Forward-looking statements

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Agenda

Paul Bolno, MD, MBA President & CEO | Wave Life Sciences	**Opening Remarks**
Michael Panzara, MD, MPH Chief Medical Officer| Wave Life Sciences	**PRECISION-HD2 topline results and clinical trial expansion**
Paul Bolno, MD, MBA President & CEO | Wave Life Sciences	**SNP3 and closing remarks**
Q&A	

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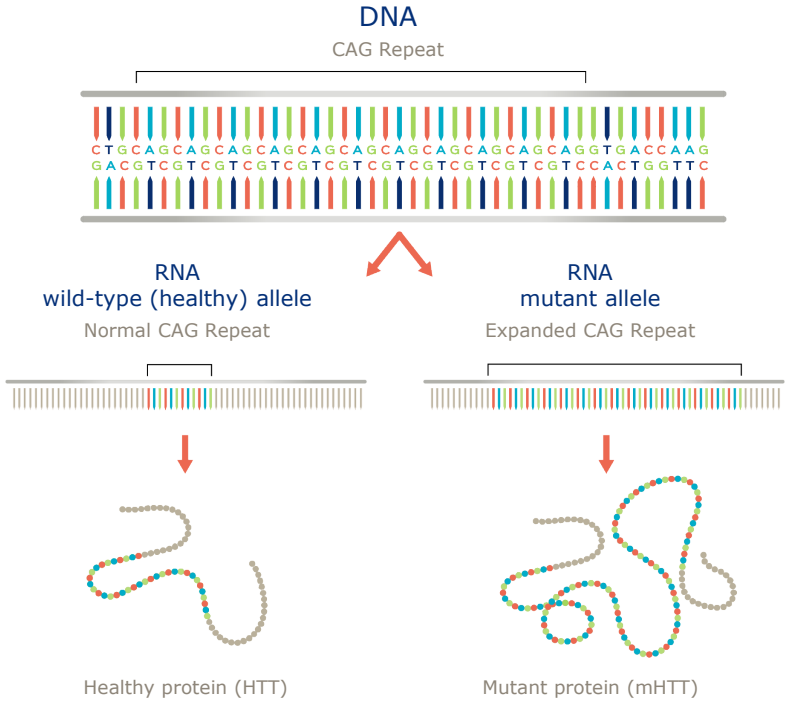
Huntington’s disease: a hereditary, fatal disorder

- Autosomal dominant disease, characterized by cognitive decline, psychiatric illness and chorea; fatal
- No approved disease-modifying therapies
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT); accumulation of mHTT causes progressive loss of neurons in the brain
- Wild-type (healthy) HTT protein critical for neuronal function; suppression may have detrimental long-term consequences
- 30,000 people with Huntington’s disease in the US; another 200,000 at risk of developing the condition

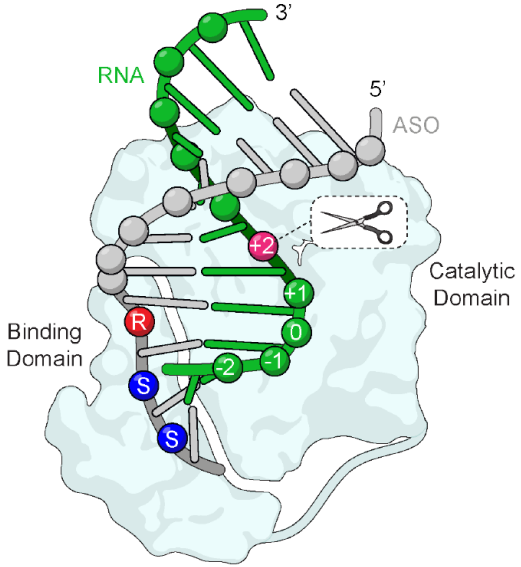


Sources: Auerbach W, et al. *Hum Mol Genet.* 2001;10:2515-2523. Dragatsis I, et al. *Nat Genet.* 2000;26:300-306. Leavitt BR, et al. *J Neurochem*. 2006;96:1121-1129. Nasir J, et al. *Cell*. 1995;81:811-823. Reiner A, et al. *J Neurosci.* 2001;21:7608-7619. White JK, et al. *Nat Genet*. 1997;17:404-410. Zeitlin S, et al. *Nat Genet*. 1995;11:155-163. Carroll JB, et al. *Mol Ther.* 2011;19:2178-2185. Huntington Disease Society of America (HDSA). What is Huntington’s disease? Available at: https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/ Accessed: November 2, 2018.

Wave approach: novel, allele-selective silencing

Aims to lower mHTT transcript while leaving healthy wild-type HTT relatively intact

- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including Huntington's disease (HD)
- Potential to provide treatment for up to 80% of HD population



RNase H and ASO:RNA

Allele-selectivity possible by targeting SNPs associated with expanded long CAG repeat in HTT gene

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Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. *Clin Genet.* 2014;86:29–36.

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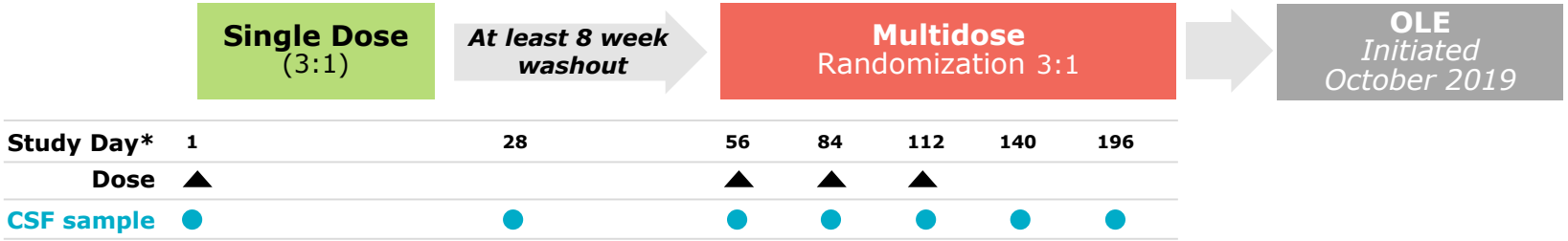
Michael Panzara, MD, MPH
Chief Medical Officer

PRECISION-HD2 clinical trial design

Phase 1b/2a trial



Multidose Cohorts

N = 12 per cohort

Expected to initiate in January 2020

As of data cut-off:

- 44 patients participated in multidose portion
- 39 had data available for mHTT assessment
  - 10 patients had not reached Day 140

OLE: Open label extension; CSF: cerebrospinal fluid
*Study day may be longer depending on patient washout period

WVE-120102 generally safe and well tolerated

- A total of 72% of those who received WVE-120102 experienced an adverse event (AE) as compared with 83% on placebo, mostly mild to moderate in intensity
- Most common AEs (those occurring in at least 10% of patients on WVE-120102) were headache, procedural pain, falls, and viral upper respiratory infection
- No serious adverse events related to treatment and no stopping rules met
- No notable changes in laboratory tests including liver or renal function tests, platelets, or markers of immune activation
- Supports the addition of higher dose cohorts

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Significant reduction in CSF mHTT
WVE-120102 compared to placebo

	Pooled Placebo (N=12)	Pooled WVE-120102 (N=27)
Median (% Change from Baseline)	9.5	-6.0
95% CI (%)	1.77, 20.38	-9.57, 4.85
Difference (%)*		**-12.4**
95% CI (%)		**-24.58, -0.40**
p-value†		**<0.05**

*Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo
†Wilcoxon-Mann-Whitney non-parametric significance test

- Pooled analysis performed for all WVE-120102 treated patients compared to placebo demonstrated 12.4% statistically significant reduction in mHTT
- Statistical analysis across treatment groups using all available data from each cohort suggests dose response at the highest doses tested (p=0.03)

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Total HTT
WVE-120102 compared to placebo

- Healthy or wild-type HTT transcript is required to produce healthy HTT protein which is important for neuronal function
- There is currently no assay available to directly measure wtHTT in the CSF
- Total HTT assay, developed by CHDI Foundation, measures total HTT protein to indirectly assess effects on wtHTT
  - With this assay, a non-allele selective, pan-silencing approach would be expected to lead to a commensurate reduction in tHTT relative to mHTT
- While there was a statistically significant reduction in mHTT compared to placebo in the topline analysis, there was no difference in tHTT compared to placebo, suggesting WVE-120102 may have a potentially differential effect on HTT
  - Wave plans to explore this with higher doses, where larger reductions of mHTT are expected and where a more discernible impact on tHTT may be observed

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wtHTT: wild-type HTT tHTT: total HTT CSF: cerebrospinal fluid

Neurofilament light chain

- Neurofilament light chain (NfL) is an indicator of axonal damage and is elevated in many neurological disorders, including Huntington’s disease
- No change in CSF neurofilament light chain (NfL) between WVE-120102 and placebo-treated groups

Byrne LM, Rodrigues FB, Johnson EB, et al. Evaluation of mutant huntingtin and neurofilament proteins as potential markers in Huntington's disease. Science translational medicine 2018;10.
CSF: cerebrospinal fluid

Advancing PRECISION-HD programs

PRECISION-HD2 (WVE-120102)

- WVE-120102 demonstrated statistically significant reduction in mutant HTT compared to placebo
- Topline data support advancing to higher doses
- No difference in total HTT or neurofilament light chain in treated patients compared to placebo
- Data from 32 mg cohort expected in 2H 2020

PRECISION-HD1 (WVE-120101)

- PRECISION-HD1 trial will remain blinded
- Additional 32 mg dosing cohort planned
- Topline results (including 32 mg cohort) now expected in 2H 2020

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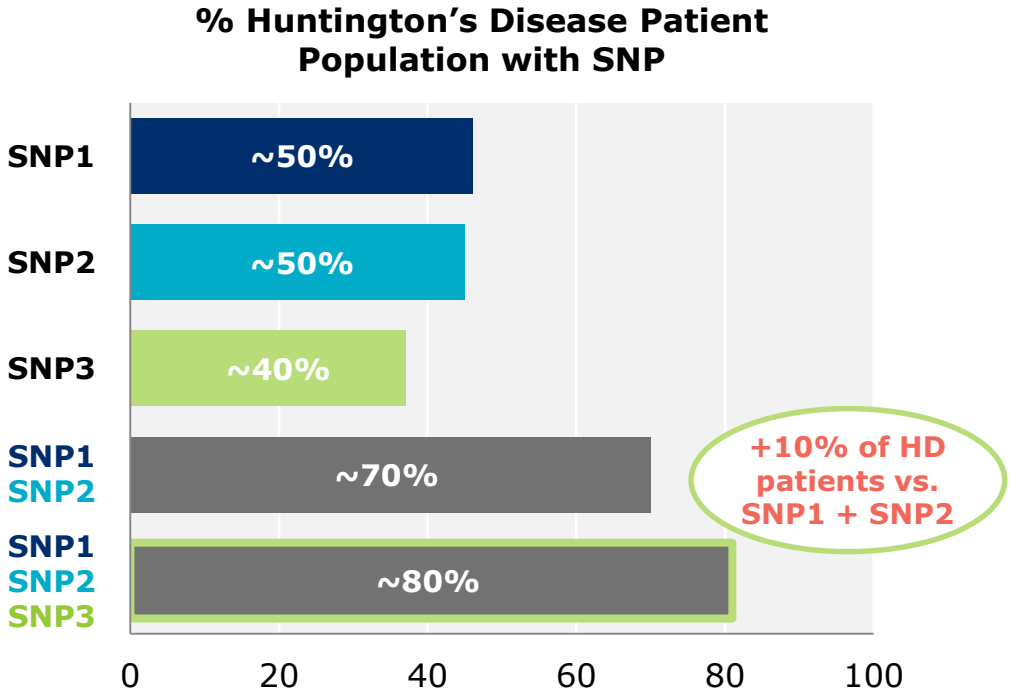
Paul Bolno
President and CEO

SNP3: Broadening reach in Huntington's disease

SNP3

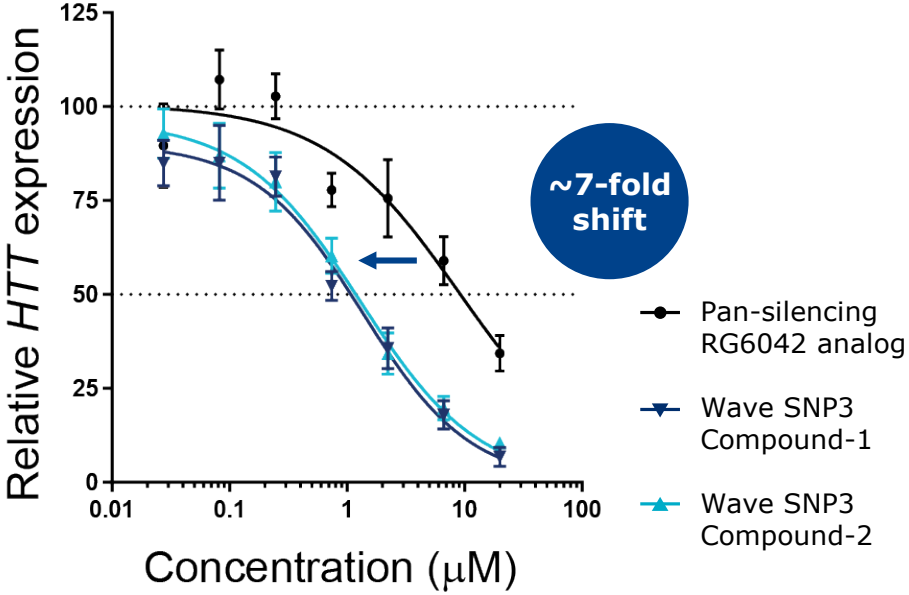
- Due to overlap, ~80% of the total HD patient population carry SNP1 and/or SNP2 and/or SNP3
- *In vivo* models for SNP3 available for preclinical development



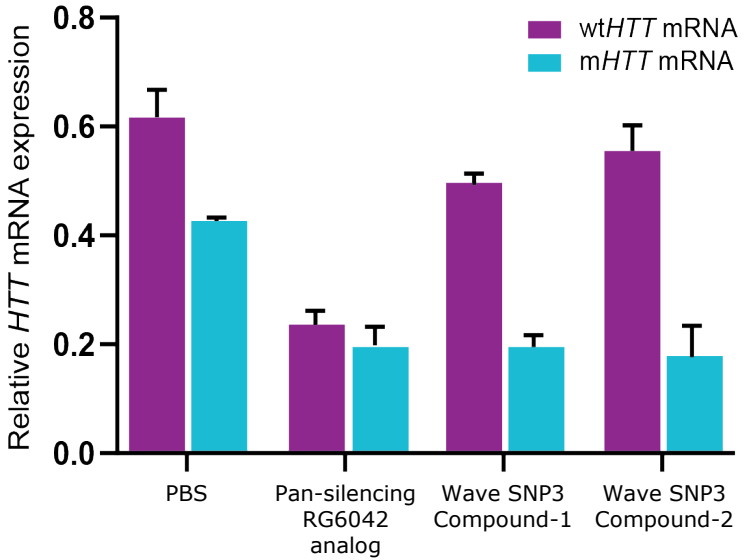
Predicted patient coverage calculated from published phasing data from Canadian HD patients (Carroll et al., 2011)

SNP3: Potent mutant HTT knockdown activity and demonstration of allele-selective silencing

Wave allele-selective compounds are more potent than pan-silencing RG6042 analog in preclinical study involving homozygous patient-derived neurons



Stereopure compounds selectively deplete mutant *HTT* mRNA in preclinical study involving heterozygous patient-derived neurons



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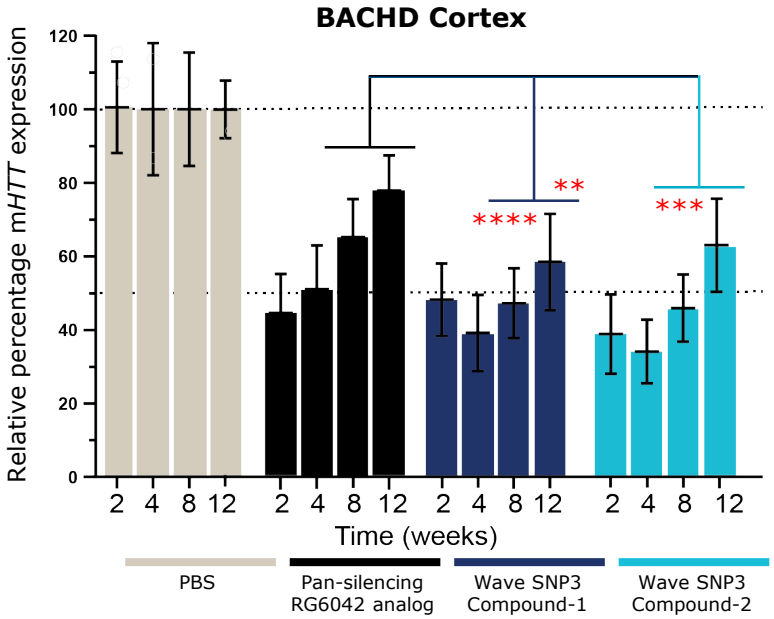
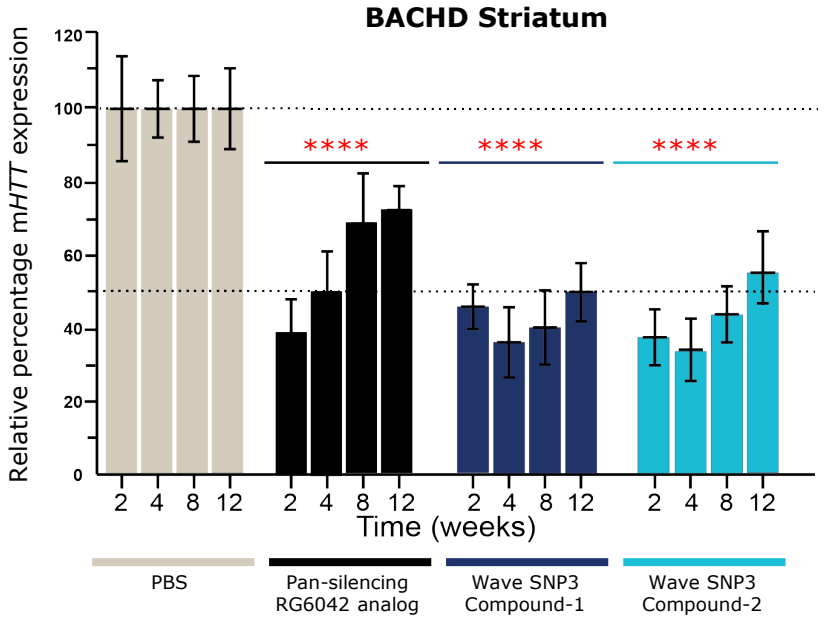
[Left] HTT mRNA remaining in iCell neurons (homozygous for SNP) incubated with the indicated ASO under free-uptake conditions. Data show mean ± sem (n=4).
[Right] Neurons were derived from GM21756 patient-derived fibroblasts (heterozygous for SNP) and treated with 20 μM of the indicated ASO under gymnotic conditions for 7 days. RNA was quantified and normalized to *TUBB3*. Data are mean ± sem (n=3). Percentage of remaining wt*HTT* and m*HTT* mRNA is indicated.

SNP3: Durable *in vivo* mutant *HTT* knockdown with stereopure compounds

Knockdown persists for 12 weeks





BACHD model only has mutant HTT (no wild-type HTT)

Oligonucleotide or PBS (3 x 100 mg ICV) was delivered to BACHD mice. Relative percentage of HTT/TUBB3 mRNA in cortex with respect to levels in PBS-treated mice is shown at 2-12 weeks post-injection. Statistics: All oligo treatment groups are statistically significantly different from PBS; One-way ANOVA ****, P≤0.0001. Wave SNP3 Compound-1 and Compound-2 are also significantly different from RG6042 analog at 8 and 12 weeks ***, P<0.005; **P=0.001.

Anticipated upcoming Wave milestones

CNS

- **2H 2020:** PRECISION-HD2 data from 32 mg cohort in Huntington's disease
- **2H 2020:** PRECISION-HD1 topline data, including 32 mg cohort, in Huntington's disease
- **2H 2020:** Initiate clinical development of SNP3 program in Huntington's disease
- **2H 2020:** Initiate clinical development of C9orf72 program in ALS and FTD

Ophthalmology

- **2020:** Advance USH2A exon-skipping program

RNA-editing

- **2020:** *In vivo* ADAR editing data

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Q&A

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