WAVE LIFE SCIENCES

SELECT HD

SELECT-HD Clinical Trial Update

September 20, 2022

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

WAVE
LIFE SCIENCES

Today’s agenda

1. **Opening remarks**
   Paul Bolno, MD, MBA, President and CEO

2. **SELECT-HD (WVE-003) clinical trial update**
   Michael Panzara, MD, MPH, CMO, Head of Therapeutics Discovery and Development

3. **Closing remarks and Q&A**

WAVE LIFE SCIENCES

Initial SELECT-HD data indicates reduction in mHTT with first wild-type sparing oligonucleotide candidate

SELECT HD

- Single doses of WVE-003 appear generally safe and well-tolerated
- CSF mHTT protein reduced following single doses (30 or 60 mg) of WVE-003
  - **Mean mHTT reduction of 22% (median 30%)** across both cohorts from baseline over 85 days
- wtHTT levels through day 85 appear consistent with allele selectivity
- Expanding single dose cohorts to optimize dose level with data expected in 1H 2023

PRISM

- **PN chemistry translation and platform validation:** Second PN chemistry containing-silencing molecule with data to indicate target engagement (WVE-003 and WVE-004) in the CNS
- Clinical data support translation of preclinical datasets
- All pipeline programs leverage similar *in vivo* modeling work

WAVE LIFE SCIENCES

mHTT: mutant huntingtin protein

wtHTT: wild-type huntingtin protein

SELECT-HD clinical trial update

Michael Panzara, MD, MPH, CMO, Head of
Therapeutics Discovery and Development

WAVE
LIFE SCIENCES

Wave innovations led to the SELECT-HD trial

SELECT HD

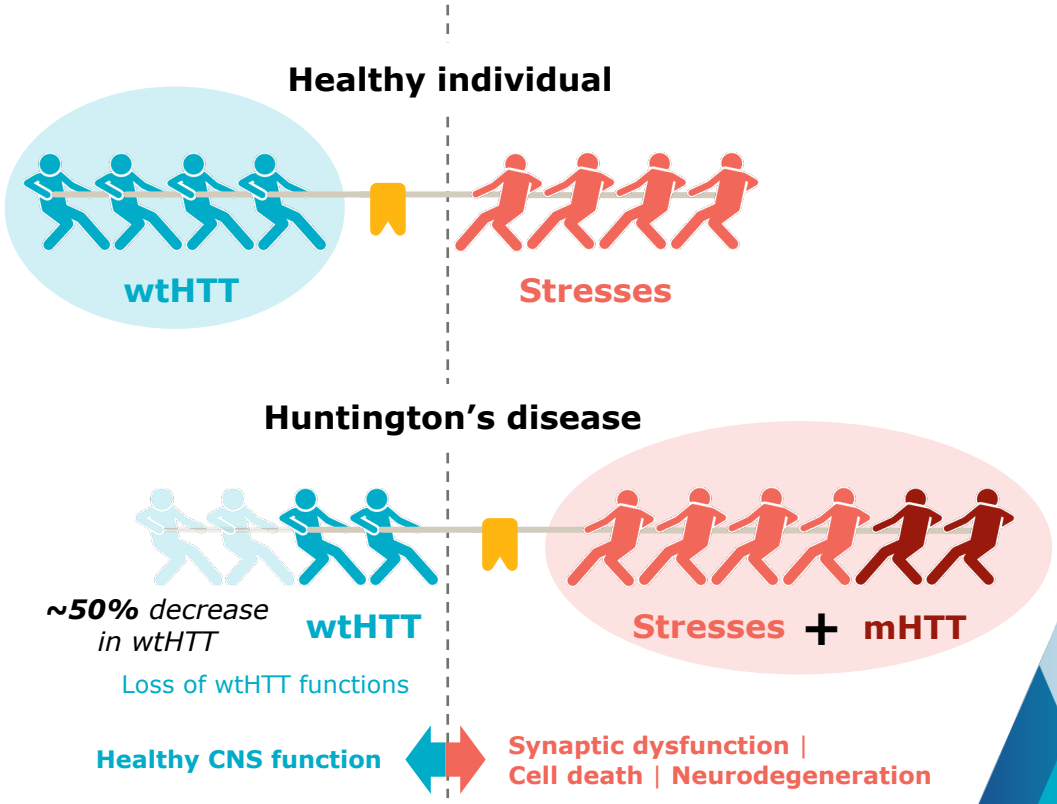
- **Advances in oligonucleotide chemistry & design:** Wave's novel PN backbone chemistry
- **Preclinical pharmacological modeling**: informed clinical starting dose
- **Ability to identify SNPs:** improved phasing assay
- **New biomarker:** development & qualification of a new wtHTT protein quantification method
- **Adaptive trial design:** enables data-driven changes to dose level & frequency while trial is ongoing

WAVE LIFE SCIENCES

Kandasamy et al., NAR Breakthrough Article, 2022 doi: 10.1093/nar/gkac037, Svrzikapa et al., Molecular Therapy Methods & Clinical Development, Dec 2020, "A Novel Quantitative Wild-type Huntingtin (wtHTT) Protein Biomarker Method for Human Cerebrospinal Fluid" poster presented at CHDI 17th Annual HD Conference 2021

mHTT toxic effects lead to neurodegeneration, loss of wtHTT functions may also contribute to HD

- Wild-type HTT (wtHTT) is critical for normal neuronal function
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT)
- Huntington's disease affects entire brain
- Monogenic autosomal dominant genetic disease; fully penetrant
- Fatal disease characterized by cognitive decline, psychiatric illness, and chorea



WAVE LIFE SCIENCES

HD: Wild-type HTT is a critical protein for important functions in the central nervous system

NEURON

Promotes neuronal survival by protecting against stress (e.g., excitotoxicity, oxidative stress, toxic mHTT aggregates)[1-8]

SYNAPSE

Plays an essential role in the transport of synaptic proteins—including neurotransmitters and receptors—to their correct location at synapses[9-12]

BRAIN CIRCUITS

Supplies BDNF to the striatum to ensure neuronal survival[13-16]

Regulates synaptic plasticity, which underlies learning and memory[17-22]

CSF CIRCULATION

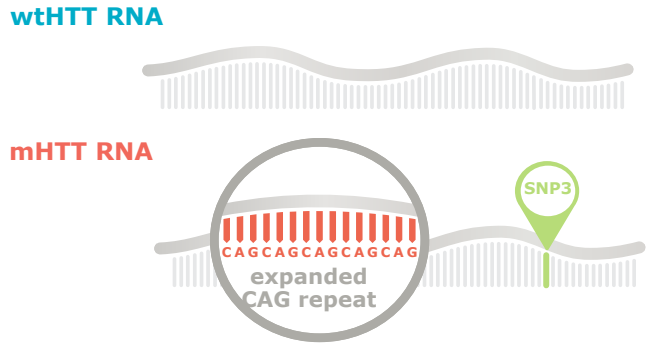
Plays a critical role in formation and function of cilia—sensory organelles that control the flow of and reabsorption of CSF—which are needed to clear catabolites and maintain homeostasis[23]

WAVE LIFE SCIENCES

BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein. 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

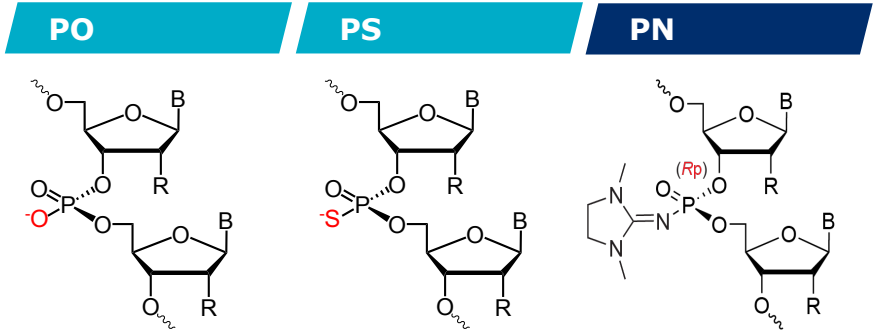
WVE-003: Investigational allele-selective oligonucleotide designed to lower mHTT while sparing wtHTT

Only wtHTT-sparing oligonucleotide in clinical development



WVE-003 targets **mHTT "SNP3",** a specific SNP found in association with the mutant allele transcript of Huntington's disease patients

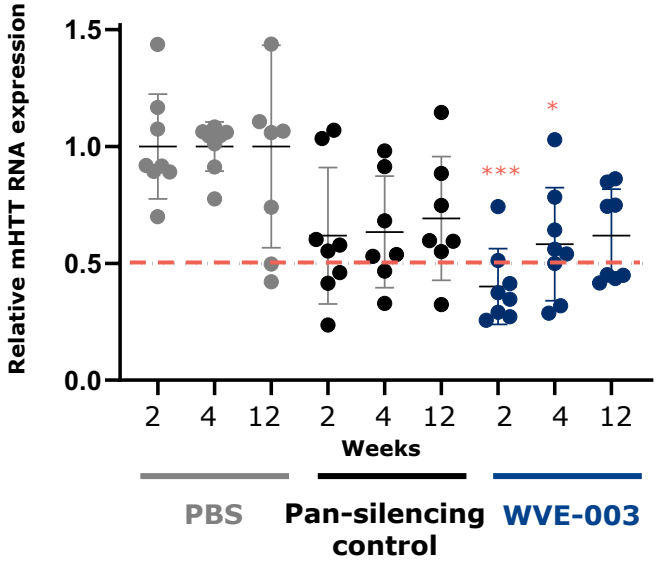
Contains Wave's novel PN chemistry



mHTT: mutant HTT; wtHTT: wild-type HTT; PO, phosphodiester; PS, phosphorothioate; PN, phosphoryl guanidine

Potent, durable and allele-selective knockdown demonstrated in preclinical studies

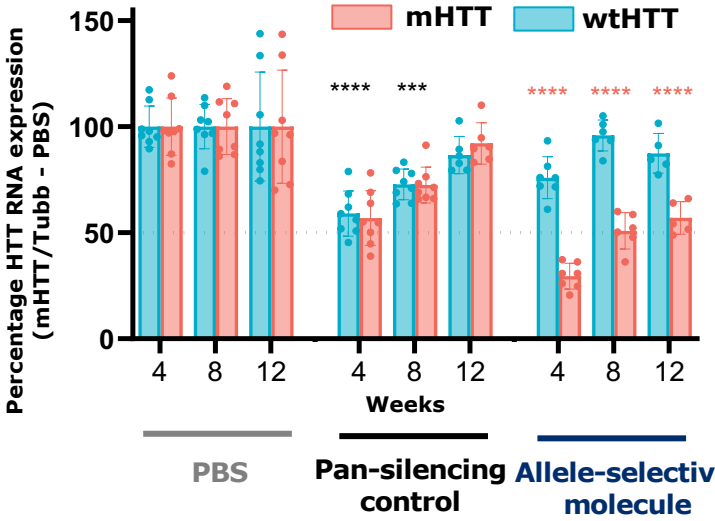
Durable mHTT knockdown for 12 weeks with multiple doses of WVE-003 in cortex of mouse model



BACHD mouse

Similar results in striatum

Multiple doses of allele-selective molecule decreases mHTT, spares wtHTT in cortex of mouse model



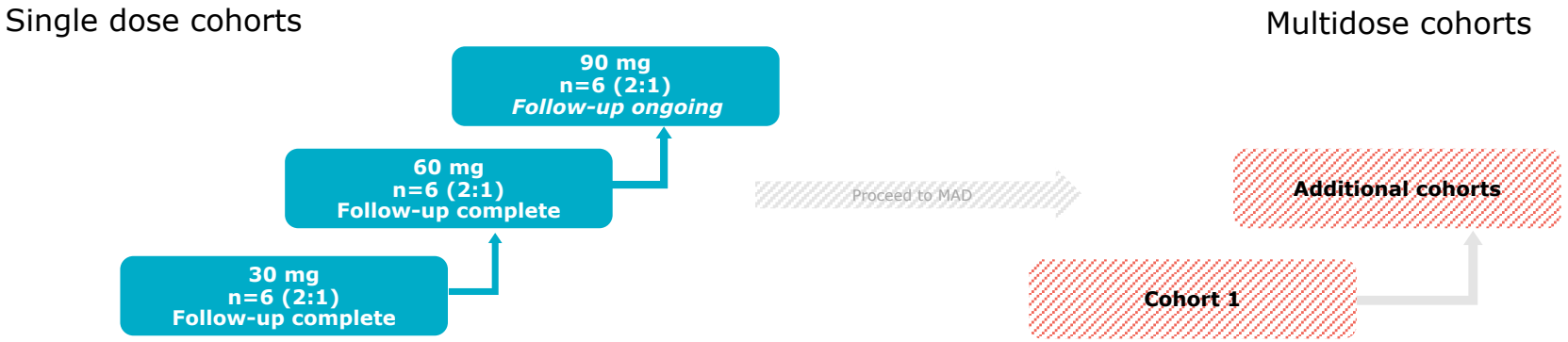
Hu97/18 mouse

Similar results in striatum

Left: 3x100 μg ICV doses in BACHD mice. Relative mHTT RNA in cortex (2, 4, 12-wks post-dosing). 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. Pan-silencing control based on Tabrizi et al, 2019 *NEJM;* Right: 3x100 μg ICV doses in Hu97/18 mice. Relative mHTT RNA in cortex at 4, 8 and 12-weeks post-dosing. Data are mean ± SD, n=8. Stats: *P<0.05, **P<0.01, ***P<0.0001, ****P<0.0001 versus PBS by 1-way ANOVA. mHTT, mutant HTT; wtHTT, wild-type HTT; Tubb, tubulin

SELECT HD: Adaptive trial designed to rapidly optimize dose level and frequency based on early indicators of target engagement

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



Single-ascending dose cohorts (SAD)

Day	1-3	15	29	57	85
Dose	▼				
PK/Biomarker Samples	●	●	●	●	●
Clinical Evaluations	●		●	●	●

Patients with Huntington's disease (HD)

Primary objectives

- Safety and tolerability

Exploratory objectives

- mHTT, wtHTT, NfL in CSF
- Clinical assessments (including MRI)

Secondary objectives

- Plasma and CSF PK profile

Inclusion criteria:

- ≥25 to ≤60 years old
- SNP3 on mHTT allele

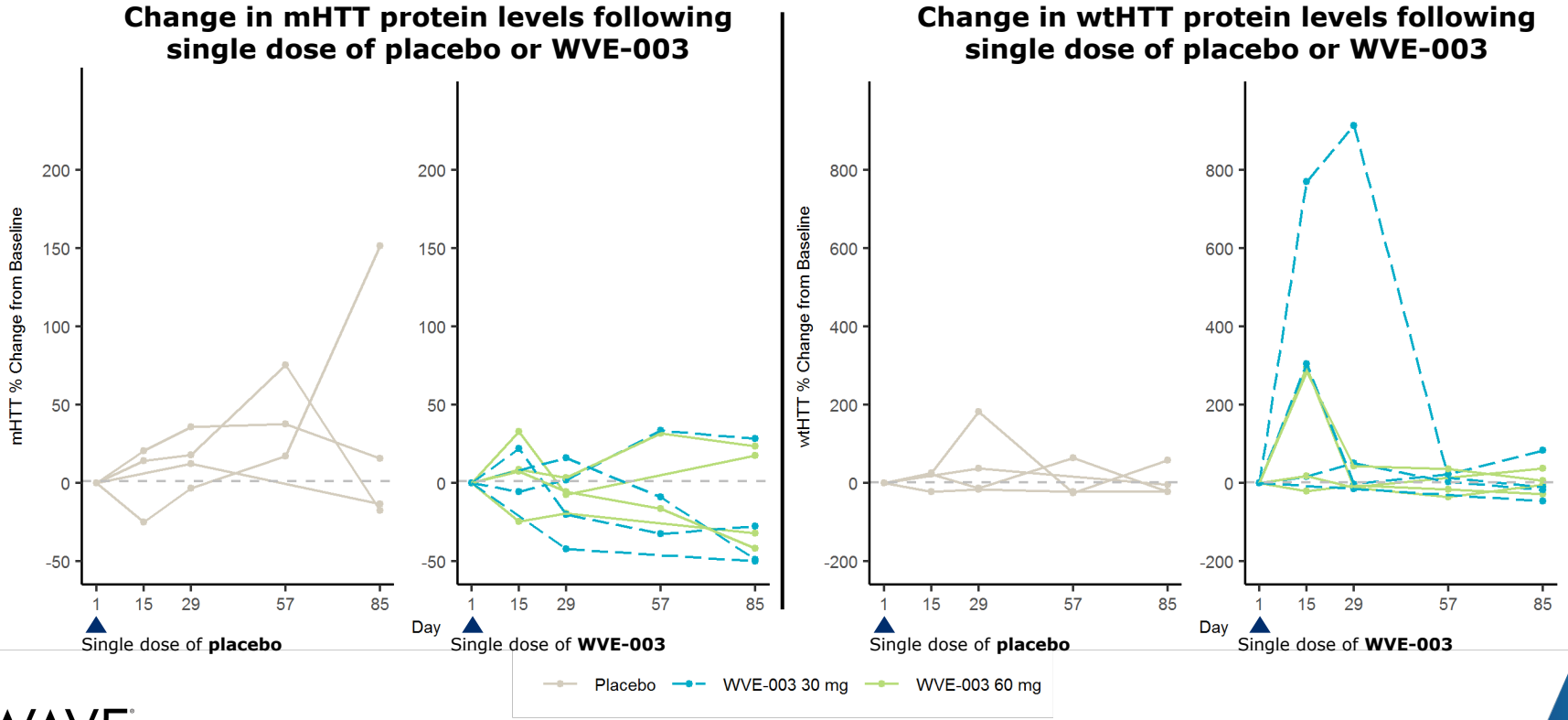
WAVE LIFE SCIENCES

Baseline characteristics generally balanced across cohorts

- A total of 18 early manifest Huntington's disease patients with confirmed SNP3 variant available for safety analysis in single dose cohorts up to 90 mg
- Baseline characteristics generally well balanced across cohorts
- No patients have discontinued from the study

WAVE LIFE SCIENCES

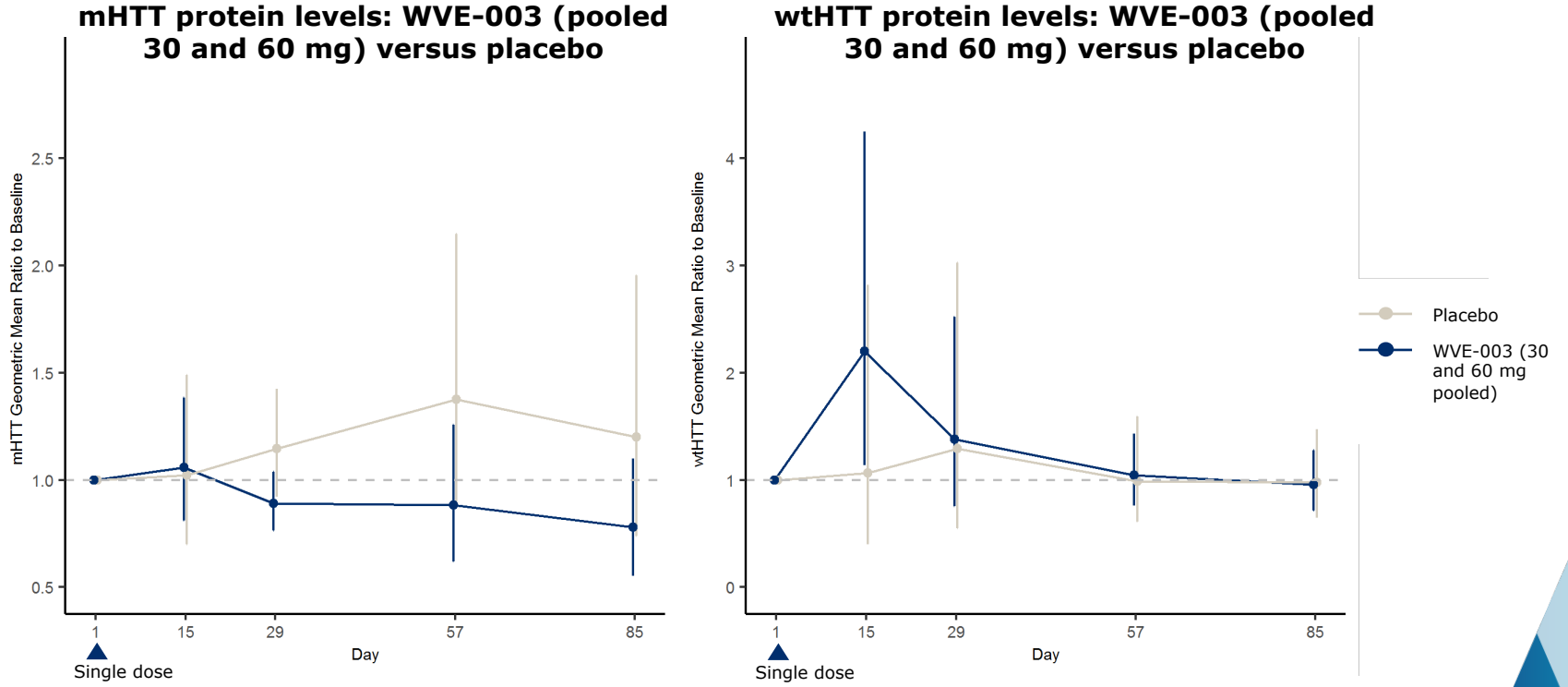
Data over 85 days suggests WVE-003 engages target in 30 and 60 mg cohorts, lowering mHTT and preserving wtHTT



mHTT: mutant huntingtin protein wtHTT: wild-type protein

Follow-up data not yet available at all timepoints in 90 mg cohort

Reductions in mean CSF mHTT and preservation of wtHTT observed in pooled analysis of single dose cohorts



At Day 85:

- 22% mean reduction in CSF mHTT from baseline
- 35% mean reduction compared to placebo

- 4% mean reduction in CSF wtHTT from baseline
- 2% mean reduction compared to placebo

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

Exploratory assessments ongoing

- Refinement of PK/PD models
- Increases in neurofilament light chain (NfL) from baseline were observed in some patients. Wave will continue to monitor trends in NfL as SELECT-HD advances
- No meaningful changes in clinical outcome measures (cUHDRS, TFC, TMS), although the dataset and duration were not sufficient to assess clinical effects

WAVE LIFE SCIENCES

TFC: Total functional capacity; TMS: Total motor score

Single doses of WVE-003 appeared generally safe and well-tolerated

- Single doses of WVE-003 up to 90 mg (n=18) appeared generally safe and well-tolerated
  - Adverse events (AEs) were balanced across treatment groups, including placebo, and all were mild-to-moderate in intensity
  - No serious adverse events (SAEs) were observed
  - No participants discontinued the study
- There were no clinically meaningful elevations in CSF white blood cell counts or protein that would indicate inflammation in the CNS

WAVE LIFE SCIENCES

Expanding single dose cohorts to optimize dose level based on initial results

- mHTT protein reductions observed in single dose cohorts
- wtHTT protein levels appear consistent with allele-selectivity
- Generally safe and well-tolerated

- Adapting clinical trial to optimize dose level

90 mg
Expanding cohort

60 mg
Expanding cohort

30 mg
Expanding cohort

Adding additional patients to each cohort

Additional single dose biomarker and safety data are expected in 1H 2023

mHTT: mutant huntingtin wtHTT: wild-type HTT

Data suggest WVE-003 engages target, lowering CSF levels of mHTT
wtHTT was preserved, which appears consistent with allele selectivity

- PN-containing stereopure compound enabled reductions in mHTT with single doses (30 or 60 mg)
- Wild-type huntingtin protein (wtHTT) levels appear consistent with allele selectivity
- Single doses appear generally safe and well-tolerated
- SELECT-HD's adaptive trial design successfully provided early indications of target engagement and safety profile to enable rapid optimization of dose level
  - Observations and modeling from preclinical models translated well in clinic

WAVE LIFE SCIENCES

Continued clinical validation of PRISM platform and PN stereochemistry

Innovative RNA therapeutics portfolio

WVE-003 HD (SNP3)	*Silencing*
WVE-004 ALS and FTD (C9orf72)	*Silencing*
WVE-N531 DMD (Exon 53)	*Splicing*
WVE-006 AATD (SERPINA1)	*RNA editing*

Innovative RNA platform PRISM Stereochemistry, PN chemistry

- ✓ **Benefits of adaptive clinical trial:** Identify target engagement and adapt to optimize dose level and frequency
- ✓ **PN chemistry translation:** WVE-003 and WVE-004 clinical data indicate target engagement in CNS
- ✓ **Platform validation:** Successfully predicted target engagement with PK/PD modeling, all pipeline programs leverage similar *in vivo* modeling work

WAVE LIFE SCIENCES

Kandasamy et al., NAR Breakthrough Article, 2022 doi: 10.1093/nar/gkac037; Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

Q&A

WAVE®
LIFE SCIENCES

WAVE®
LIFE SCIENCES

Realizing a brighter future for people affected by genetic diseases

For more information:
Kate Rausch, Investor Relations
krausch@wavelifesci.com
617.949.4827