Update on SELECT-HD: An Allele-selective Mutant Huntingtin Lowering Approach in Huntington's Disease

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SUMMARY

- Wave Life Sciences is evaluating WVE-003 for the treatment of Huntington's disease (HD).
- WVE-003 is an investigational allele-selective oligonucleotide that was designed to target a single nucleotide polymorphism (SNP3) that is associated with the mutant huntingtin allele (mHTT), enabling allele-selective lowering of mHTT and preservation of wild-type HTT (wtHTT).[1]
- We established ~30% lowering of mHTT in cerebrospinal fluid (CSF) as the threshold for advancement of WVE-003.
  - Based on data from preclinical models, ~50% lowering of mHTT in CNS tissue is expected to yield benefit.[2]
  - In clinical trials, changes in mHTT protein are measured in CSF, where reductions are smaller than those in CNS tissues. 30% mean lowering of mHTT in CSF has been associated with ~50% lowering in CNS tissue.[3]
- SELECT-HD (NCT05032196) was a Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of WVE-003 in adult patients with early manifest HD who carry the targeted SNP3.[4]
- In SELECT-HD, 30 mg WVE-003 dosed every 8 weeks led to a maximum mean mHTT reduction of 46% compared with placebo at day 169, or 8 weeks following the last dose. Reductions were durable, with 44% lowering persisting to day 197, or 12 weeks post last dose. Thus, WVE-003 met the mHTT CSF-lowering threshold that is expected to yield clinical efficacy with substantial margin.
- Using data from SELECT-HD and a population PK/PD model that describes the relationship between WVE-003 and mHTT levels in CSF following intrathecal (IT) administration of WVE-003, we predict that 30 mg WVE-003 dosed every 12 weeks (quarterly) will support mHTT-lowering that meets the threshold expected to yield clinical efficacy in HD.

INTRODUCTION

- WVE-003 is an investigational allele-selective oligonucleotide designed to lower mHTT expression and preserve wtHTT by targeting a heterozygous variant in the *HTT* transcript called SNP3.[1]
- WVE-003 is administered via IT injection by lumbar puncture.
- WVE-003 was evaluated in SELECT-HD, a two-part Phase 1b/2a clinical trial, that ended in June 2024 (**Figure 1**).
  - In the single-dose phase of SELECT-HD, participants were randomized 2 to 1, active to placebo. In the active groups, participants received 30, 60, or 90 mg of WVE-003. CSF samples for PK and PD assessments were collected pre-dose on day 1, and then on days 15, 29, 57, and 85 (**Figure 1**).
  - In the multidose phase, participants were randomized as in the single-dose phase. In the active cohort participants received 3 doses of 30 mg WVE-003 every 8 weeks. CSF samples for PK and PD assessments were collected pre-dose (as above) and on days 29, 57, 85, 113, 141, 169, and 197 (**Figure 1**).
- We analyzed 263 CSF samples (**Table 1**).
  - WVE-003 concentrations were analyzed using a validated LC-MS method with a lower limit of quantification (LLOQ) of 2 ng/mL. PK samples with missing values were excluded. These samples typically were not collected. Samples that were below quality limit (BQL) were replaced with zero and flagged as such.

Figure 1. SELECT-HD, design and CSF sample collection

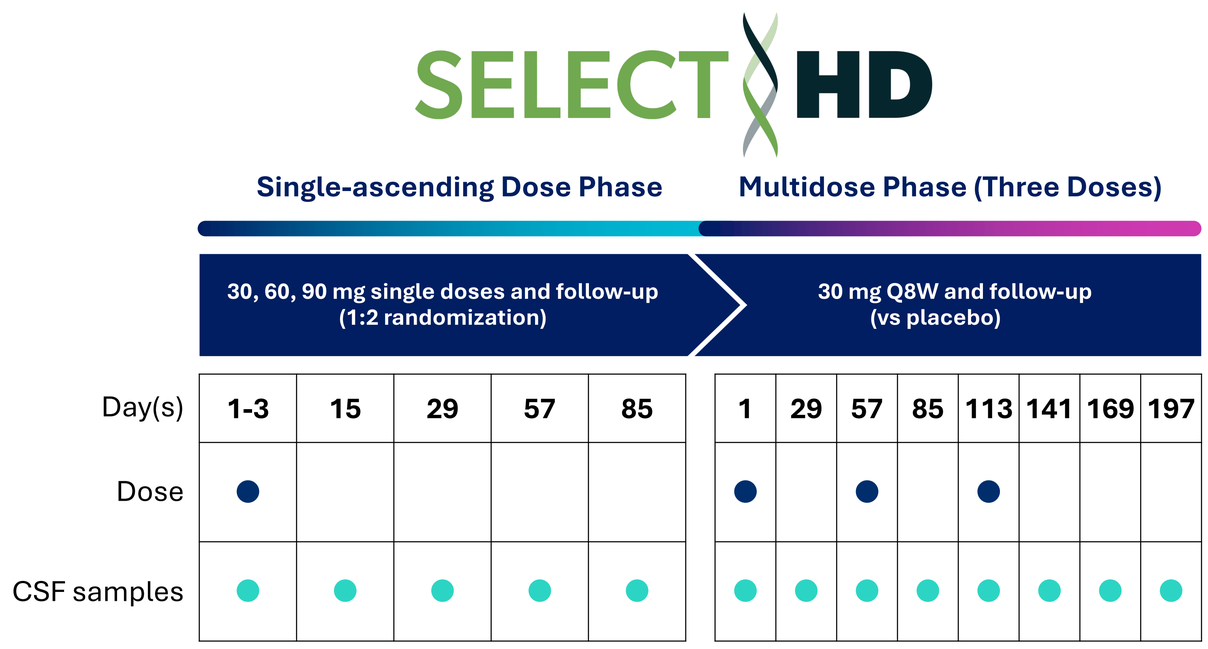
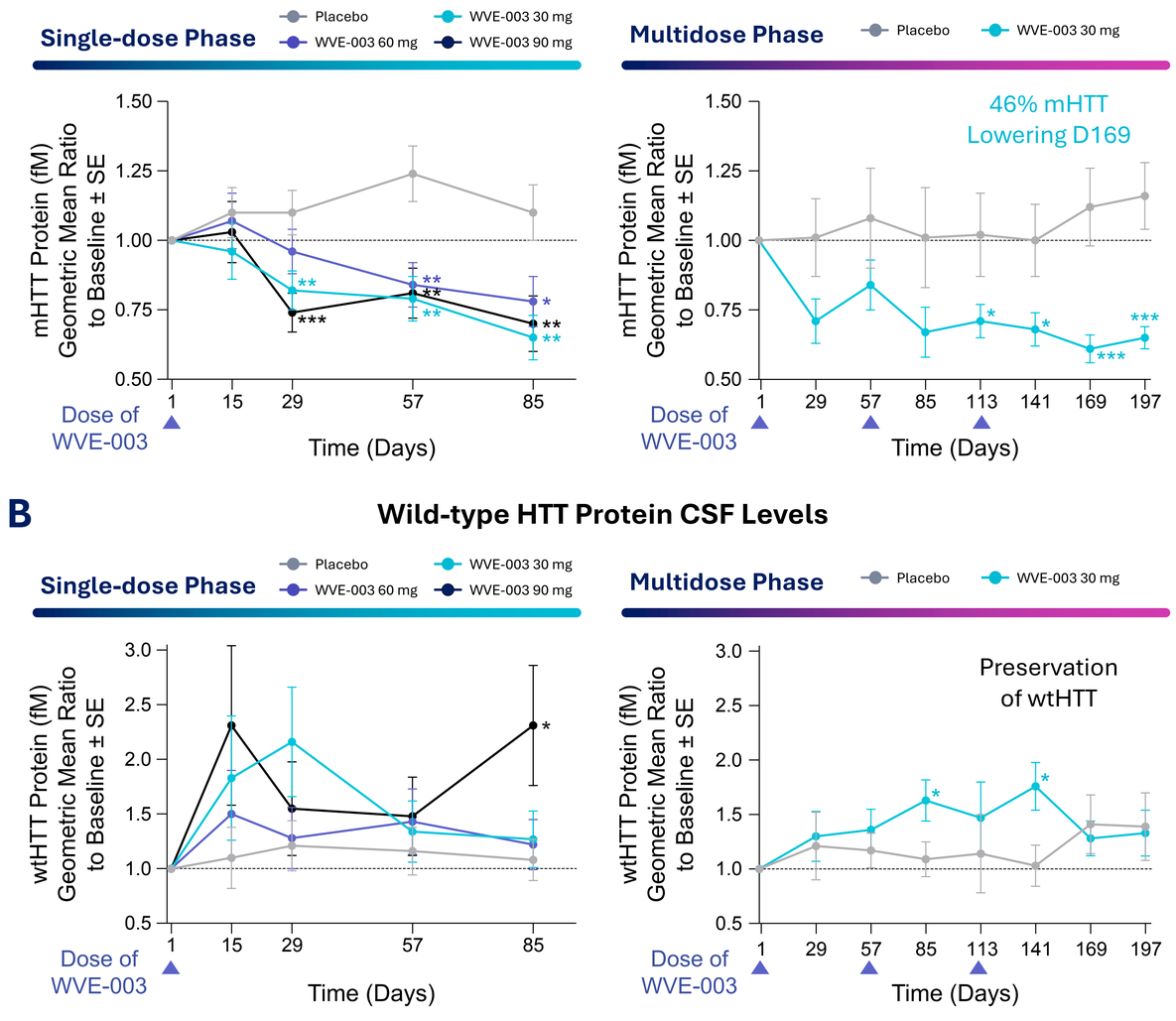


Table 1. Summary of CSF samples collected in SELECT-HD

Phase	Treatment	No patients
Single-dose	Placebo	**15**
	30 mg WVE-003	**13**
	60 mg WVE-003	**10**
	90 mg WVE-003	**8**
Multidose	Placebo	**7**
	30 mg WVE-003	**16**

RESULTS

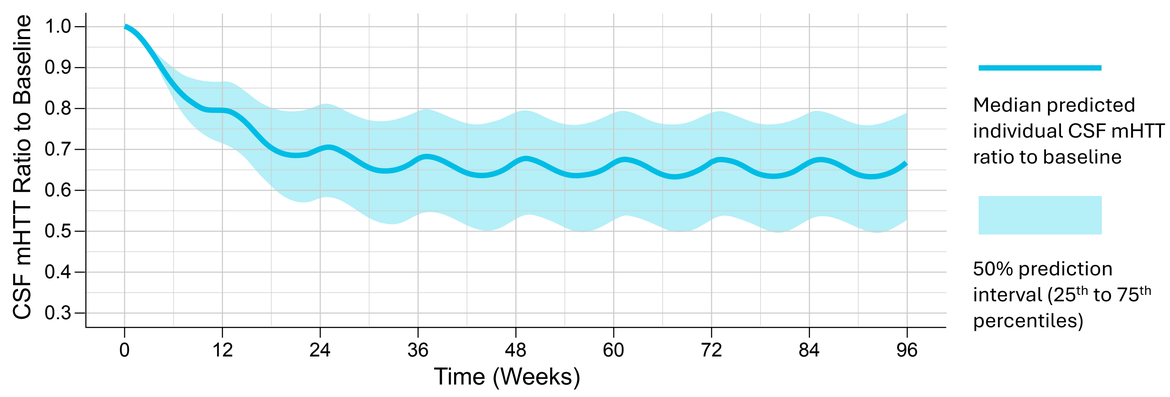
Figure 2. WVE-003 led to significant and durable allele-selective mHTT lowering in single-dose and multidose phases of SELECT-HD



mHTT and wtHTT concentrations in CSF samples were analyzed using validated LC-MS methods.[5-14] Stats: * p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. mHTT: mutant huntingtin protein; wtHTT: wild-type huntingtin protein.

- In the single-dose phase, WVE-003 led to significant mHTT lowering with ≥30% maximum mean lowering at day 85 compared with placebo for all doses. There was no apparent dose-response (**Figure 2A**, left).
- In the multidose phase, 30 mg WVE-003 dosed every 8 weeks led to significant mHTT lowering reaching ≥30% mean mHTT lowering compared with placebo by day 113. A maximum reduction in mHTT was observed at day 169 (46% vs placebo), with 44% reduction (vs. placebo) persisting to at least day 197, 12 weeks post-last dose (**Figure 2A**, right).
- Preservation of wtHTT levels in CSF at or above baseline and placebo levels throughout the study in the single and multidose phases confirmed the allele-selective mechanism for WVE-003 (**Figure 2B**).
- These data demonstrate that the lowest single dose level of WVE-003 evaluated (30 mg) achieved ≥30% mean mHTT CSF lowering, and multiple doses resulted in substantial, selective and durable mHTT-lowering in CSF.

Figure 3. Prediction from the PK/PD model indicate mHTT CSF lowering exceeding 30% with 30 mg Q12W regimen



PK/PD modeling software used Phoenix. Phoenix dataset assembly was performed in SAS and R (Version 4.0.5 or later).[15] Post-modeling analysis was performed using R v4.0.5.

- WVE-003 CSF PK was modeled using a one-compartment model with linear elimination, and the dose proportionality was modeled using a power function.
- We tested the model against PK/PD data observed in SELECT-HD, and the model predictions were aligned with the observed data. We performed Monte Carlo simulations using the final PK/PD model to predict CSF mHTT lowering following 30 mg IT administration at variable frequencies.
- The PK/PD model predicts median mHTT lowering of ~35% in the CSF.
- The model predicts that 30 mg WVE-003 dosed quarterly will support mHTT-lowering that meets the prespecified ≥30% CSF mHTT threshold, which is predicted to yield deeper mHTT lowering in CNS tissue and lead to clinical efficacy in HD (**Figure 3**).

References: 1. Iwamoto, et al., 2024. *Mol Ther Nucleic Acids* 35(3):102246. doi: 10.1016/j.omtn.2024.102246; 2. Kordasiewicz, et al., 2012. Neuron 74(6):1031-44. doi: 10.1016/j.neuron.2012.05.009; 3. Norris, et al., 2020. HD Therapeutics conference. Development of a non-clinical pharmacokinetic/pharmcodynamic model to predict CSF reductions in huntingtin protein in individuals with Huntington's disease; 4. https://ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-announces-positive-results-phase-1b2a-select; 5. Wild, et al., 2015. *J Clin Invest*. DOI: 10.1172/JCI80743; 6. Byrne, et al., 2018. *Sci Transl Med.* DOI: 10.1126/scitranslmed.aat7108; 7. Rodrigues, et al., 2020. *Sci Transl Med.* DOI: 10.1126/scitranslmed.abc2888; 8. Fodale, et al., 2017. *J Huntingtons Dis.* DOI: 10.3233/JHD-170269; 9. Tabrizi, et al., 2019. *N Engl J Med.* DOI: 10.1056/NEJMoa1900907; 10. Fodale, et al., 2020. *Sci Rep.* DOI: 10.1038/s41598-020-78790-5; 11. Vauleon, et al., 2023. *Sci Rep.* DOI: 10.1038/s41598-023-32630-4; 12. McColgan, et al., 2023. *N Engl J Med*. DOI: 10.1056/NEJMc2300400; 13. Boyanapalli, et al., 2022. A novel quantitative wild-type huntingtin (wtHTT) protein biomarker method for human cerebrospinal fluid. Abstract presented at 17th Annual HD Therapeutics Conference; 14. Haegele, et al., 2024. Assays to Evaluate an Allele-selective Approach for Lowering Mutant Huntingtin in Clinical Trials. Abstract presented at the 19th Annual HD Therapeutics Conference;15. http://www.r-project.org/. **Affiliations:** MP was an employee and consultant of Wave Life Sciences during the design and conduct of the study. AMLKC was an employee of Wave Life Sciences during the design and conduct of the study. **Acknowledgments:** This work was funded by Wave Life Sciences. We are grateful to SELECT-HD study participants and their families, as well as all investigators who contributed to the clinical trial. Darienne Myerbeck (Wave Life Sciences) provided editorial support and Eric Smith provided graphical support for this poster.