SELECT-HD: Evaluating Allele-Selective Mutant Huntingtin Lowering in Huntington's Disease

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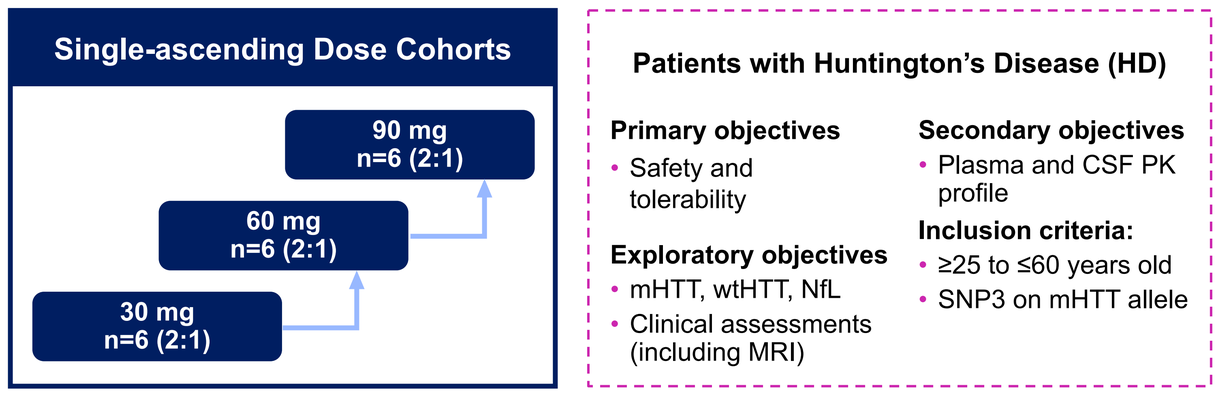
SUMMARY

- We are advancing WVE-003, an investigational allele-selective mHTT-lowering oligonucleotide, in a phase 1b/2a clinical trial called SELECT-HD (NCT05032196)[1] in patients with early manifest Huntington's disease (HD).
- WVE-003 is designed to target a single nucleotide polymorphism (SNP3) that is associated with the mutant allele of *HTT* (*mHTT*), enabling allele-selective lowering of *mHTT* and preservation of wild-type HTT (*wtHTT*).[2]
- In September 2022, Wave reported data from the first 18 participants who had received a single dose of WVE-003 (30 mg, n=4; 60 mg, n=4; 90 mg, n=4; placebo, n=6).[3] Herein, we review the SELECT-HD data presented in September 2022.
- The mean reduction in CSF mHTT compared with placebo was 35% (+18%—64%, 95% CI) at 85 days following a single dose in participants enrolled in the 30 and 60 mg cohorts. The mean reduction in CSF mHTT compared with baseline was 22% (+10%—-45%, 95% CI).
- In these cohorts, wtHTT protein levels appeared consistent with allele selectivity.
- Single doses of WVE-003 up to 90 mg appeared generally safe and well-tolerated, with no serious adverse events (SAEs) or participant discontinuation.
- Early data from the SELECT-HD trial provide early indications for target engagement and a favorable safety profile for WVE-003, enabling Wave to adaptively expand the single-dose cohorts and initiate a multidose cohort (30 mg dosed every eight weeks).
- Pharmacodynamic and safety data from the 30 mg multi-dose cohort with extended follow-up, along with single-dose data, are expected in the second quarter of 2024.

INTRODUCTION

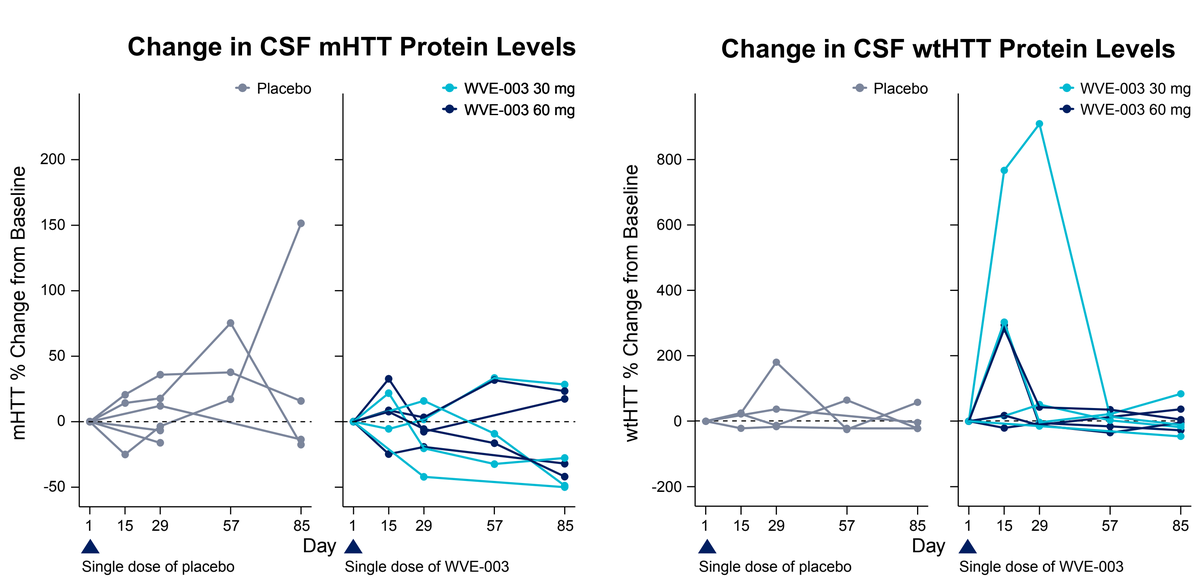
- SELECT-HD is a placebo-controlled phase 1b/2a clinical trial to assess the safety and tolerability of single- and multiple-ascending intrathecal doses of WVE-003 in people with a confirmed diagnosis of early-stage HD carrying SNP3 in association with the CAG expansion mutation (**Figure 1**). The study will also assess pharmacology of WVE-003, biomarkers and clinical endpoints.
- In the initial SELECT-HD single-dose cohorts, patients were randomized 2 to 1, active to placebo, into cohorts of 6 patients.
- Before each dose escalation, the independent DSMB reviewed unblinded pharmacokinetic (PK), biomarker, and clinical data to determine the next single dose to be given. Biomarker analyses at multiple timepoints provided the data for these reviews, and patients in each cohort are followed for 85 days, or approximately 12 weeks.
- Wave shared initial data from SELECT-HD in September 2022 that was based on 3 single-dose cohorts: 30, 60, and 90 mg. The data included CSF biomarker data from the 30 and 60 mg cohorts out to day 85 and safety data up to and including the 90 mg cohort.

Figure 1. SELECT-HD is an ongoing adaptive clinical trial designed to rapidly optimize dose level and frequency based on early indicators of target engagement



RESULTS

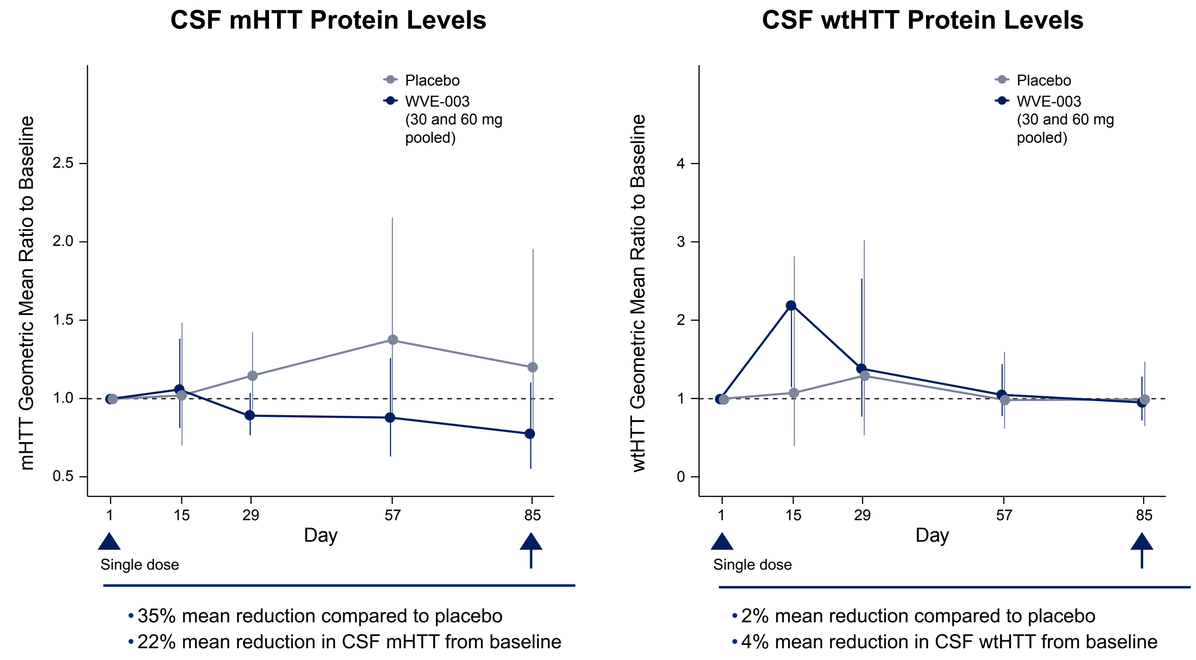
Figure 2. Data from single 30- and 60-mg dose cohorts suggest mHTT lowering, wtHTT sparing by day 85



mHTT: mutant huntingtin protein; wtHTT: wild-type protein. Follow-up data for 90 mg cohort is incomplete.

- Data showing mHTT protein decreasing in CSF over 85 days suggests WVE-003 engages target in the 30 and 60 mg cohorts (**Figure 2**).
- Over the same 85 days, wtHTT levels in CSF were consistent with allele selectivity.

Figure 3. Pooled data from single-dose cohorts suggest reductions in mean CSF mHTT, preservation of wtHTT



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

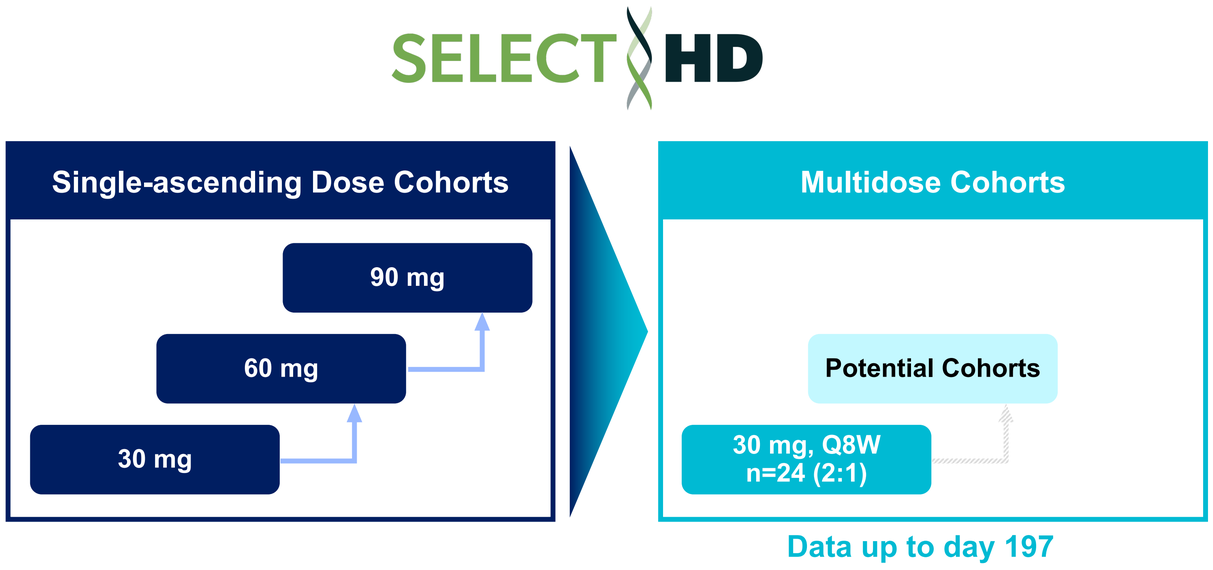
- As there did not appear to be a dose response, results from the 30 and 60 mg cohorts were pooled for further analyses (**Figure 3**).
- Over 85 days, WVE-003 led to a 35% (+18%—64%, 95% CI) mean reduction in CSF mHTT compared with placebo. As compared with baseline, the mean difference was 22% over the same time.
- The effect of WVE-003 on wtHTT protein levels in the pooled results from the 30 and 60 mg cohorts were clearly different from mHTT, suggesting preservation of wtHTT over 85 days.
- These data are consistent with the intended allele-selective mechanism for WVE-003.
- Some patients experienced elevations in CSF NfL, but they were not dose-dependent.

Table 3. Single doses of WVE-003 appeared generally safe and well-tolerated*
(*through data cut for Sept. 2022 readout)

		WVE-003			
No. participants with: n (%)	**Pooled placebo (n=6)**	**30 mg (n=4)**	**60 mg (n=4)**	**90 mg (n=4)**	**Pooled active (n=12)**
Any TEAE	3 (50)	2 (50)	4 (100)	4 (100)	10 (83.3)
Mild	3 (50)	2 (50)	4 (100)	4 (100)	10 (83.3)
Moderate	1 (16.7)	0 (0)	1 (25)	2 (50)	3 (25)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TEAE related to study drug	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinued/ withdrawn due to TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

- Single doses of WVE-003 up to 90 mg (n=18) appeared generally safe and well-tolerated (**Table 1**).
- 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, and 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.
- The study is monitored by an unblinded independent Safety Monitoring Committee who assess the benefit-risk profile in an ongoing fashion. The multi-dose phase is progressing well with data expected in the second quarter of 2024.

Figure 4. SELECT-HD adaptations and next steps



- Based on data released in September 2022, SELECT-HD has been adapted to expand the size of the single-dose cohorts and to include a 30 mg, Q8W multidose cohort (**Figure 4**). These adapted cohorts are now fully enrolled. Biomarker and safety data for all ongoing cohorts are expected in the second quarter of 2024.

References: 1. https://clinicaltrials.gov/study/NCT05032196?term=NCT05032196&rank=1; 2. Liu et al., Preclinical evaluation of stereopure antisense oligonucleotides for allele-selective lowering of mutant HTT. Manuscript submitted; 3. https://ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-announces-positive-update-phase-1b2a-select. **Acknowledgments:** The authors are grateful to all the patients, families, and advocacy organizations who collaborated with Wave, particularly the study participants and families involved in SELECT-HD. The authors are grateful to all SELECT-HD study investigators, the Clinical Advisory Committee (Daniel Claassen, Mary Edmondson, Ray Dorsey and Ralf Reilmann), and other collaborators who have been essential to study execution. Amy Donner (Wave Life Sciences) and Eric Smith provided editorial and graphical support, respectively.