



December 30, 2019

Dear global HD community,

Today we announced encouraging topline results from PRECISION-HD2, our ongoing Phase 1b/2a placebo-controlled trial evaluating the investigational therapy WVE-120102 targeting SNP2. In an analysis of the study results, we compared all patients treated with WVE-120102 to patients who received placebo and saw a statistically significant reduction of 12.4% ($p < 0.05$) in mutant huntingtin protein in the cerebrospinal fluid (CSF).

In addition to demonstrating a reduction in mutant huntingtin protein, WVE-120102 was generally safe and well-tolerated across all patients, so we are exploring optimal dosing and expect to add an additional treatment group to the ongoing Phase 1b/2a study at a higher dose (32 mg) in January to evaluate effects on mutant huntingtin protein. We are also adding an additional treatment group to our other Phase 1b/2a study called PRECISION-HD1, evaluating the investigational therapy WVE-120101 targeting SNP1. We now expect to share results from both studies including the 32 mg doses in the second half of 2020.

We are deeply committed to the HD community. In addition to the PRECISION-HD studies, we are developing other potential treatments for the disease, advancing the understanding of wild-type huntingtin preservation, and supporting the needs of people living with HD.

All of us at Wave are enormously grateful to the PRECISION-HD clinical trial participants and their families. We recognize the personal sacrifices made by each-and-every family involved in these trials. Their participation along with the support of the entire HD community are critical to advancing the scientific and medical understanding required to defeat this devastating disease.

Sincerely,

A handwritten signature in black ink, appearing to read "Michael Panzara", with a long, sweeping tail extending to the right.

Michael Panzara, MD, MPH
Chief Medical Officer

Frequently Asked Questions

What are the two investigational therapies being studied in the PRECISION-HD program?

WVE-120101 and WVE-120102 are investigational stereopure antisense oligonucleotides designed to selectively target the mutant huntingtin (HTT) mRNA transcript of SNP rs362307 (SNP1) and SNP rs362331 (SNP2), respectively. SNPs, or single nucleotide polymorphisms, are naturally occurring variations within a given genetic sequence and in certain instances can be used to distinguish between two related copies of a gene (also called "alleles") where only one is associated with the expression of a disease-causing protein. This is called an allele-selective approach. *In vitro* studies in patient-derived cell lines have shown that WVE-120101 and WVE-120102 selectively reduce levels of mutant HTT mRNA transcript and protein, while leaving wild-type, or healthy, HTT mRNA transcript and protein relatively intact. Accumulation of mutant HTT causes progressive loss of neurons in the brain and is thought to be the underlying cause of Huntington's disease. The healthy transcript is required to produce healthy HTT protein, which is critical for neuronal function, as evidenced by multiple preclinical studies indicating that long-term suppression of healthy HTT protein may have detrimental consequences.

What is the PRECISION-HD program?

Our PRECISION-HD program is the first clinical program to use an allele-selective approach to target the underlying cause of Huntington's disease. PRECISION-HD1 and PRECISION-HD2 are Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled clinical trials evaluating the safety and tolerability of WVE-120101 and WVE-120102, respectively.

Will you initiate a Phase 3 clinical trial of WVE-120102?

Our current focus is on delivering the 32 mg dataset in the second half of 2020.

We would anticipate working on continued development of WVE-120102 including Phase 3 studies if the data from the ongoing study continue to support it.

How can I enroll in the new treatment groups for the PRECISION-HD trials?

We expect to enroll patients into the 32 mg treatment group primarily at sites that participated in the multi-dose portion of the Phase 1b/2a PRECISION-HD2 study, which only enrolled patients outside of the U.S. If you have questions about participating in a clinical trial we encourage you to speak directly with your physician.

What happens now to the patients who are in the trial, what dose are they being given?

In October 2019, we initiated an open-label extension (OLE) study, which is open to patients outside the United States. Initially patients will continue on their existing doses except for the 2 mg cohort where they will receive 4 mg.