Disappointing Results from Wave's PRECISION-HD1 and 2 Trials

Wave Life Sciences shared the disappointing news that their two ASOs in Phase 1/2 trials in HD patients did not successfully lower mutant huntingtin.

By Dr Rachel Harding and Dr Leora Fox | **March 30, 2021** | **Edited by Dr Rachel Harding**

The Huntington's Disease community faced more disappointing news this week as Wave Life Sciences shared that they will discontinue development of two ASOs they had been testing in people with HD. Designed to decrease harmful huntingtin protein while keeping the healthy form intact, these experimental therapies unfortunately did not have the expected huntingtin-lowering effect. Wave will not move forward with these two ASOs, but is planning a clinical trial of a third ASO with new and improved chemistry. Let's talk more about what this means, what's next for Wave, and how this relates to the recent news from (Roche)[https://en.hdbuzz.net/300].

What was the aim of the PRECISION-HD1 and 2 trials?

Wave developed ASOs (antisense oligonucleotides) called WVE-120101 and WVE-120102 which they hoped would specifically lower the harmful form of huntingtin made in people with HD. ASOs work by interfering with the genetic message telling cells in our body to make a specific protein molecule. The ASOs developed by Wave specifically target the message for the harmful form of the huntingtin protein, preserving the message for the healthy form, so only levels of harmful huntingtin should be lowered. This differs from other huntingtin lowering approaches, such as those used by Roche and uniQure, which lower both the healthy and the harmful forms of huntingtin. Scientists at Wave think this is important as the healthy huntingtin protein remains to do its job properly, whilst the harmful form of the protein is eliminated so it can't misbehave.

Unfortunately, in the PRECISION-HD trials, there was no significant change in the levels of the harmful huntingtin protein in trial participants treated with Wave ASOs, compared to those treated with placebo.

Image credit: Africa Studio

During the PRECISION-HD1 and PRECISION-HD2 trials, up to 88 participants per trial received four monthly doses of ASO or placebo, delivered by injection into the spinal column. These relatively short Phase 1b/2a trials were testing safety and the drugs' ability to lower harmful huntingtin - they were not designed to measure effects on symptoms of HD. At the end of the trial, participants could decide to continue receiving monthly doses of the drug - this is known as an open-label extension. While the dosing period for the PRECISION-HD1 and PRECISION-HD2 trials had already ended, each study had an open-label extension ongoing.

So what happened in these trials?

On March 29th, Wave shared a press release sharing the key findings from the PRECISION-HD trials. Unfortunately, in the PRECISION-HD2 trial, there was no significant change in the levels of the harmful huntingtin protein in trial participants treated with WVE-120102,

compared to those treated with placebo. In the open-label extension study, in which participants continued to receive monthly doses of ASO, some for nearly a year, only very small reductions of harmful huntingtin protein were measured.

The PRECISION-HD1 study began a little later than the PRECISION-HD2 study, and though dosing of WVE-120101 had finished, Wave needs a few more months to include the highest dose group in their analysis. However, based on the data they have from lower doses, similarly disappointing huntingtin-lowering results were seen for the PRECISION-HD1 trial. For this reason, Wave will discontinue development of WVE-120101 and WVE-120102. Participants in the open-label extension studies will have a final follow-up visit, but there will be no further doses.

Based on side effects in the drug and placebo groups, both drugs were safe and well tolerated, with a small percentage of participants who experienced severe side effects. However, neither ASO did in humans what it was designed to do: lower mutant huntingtin levels.

What's next for Wave?

Another piece of more promising news shared in the press release was that Wave plans to move forward with a trial of a third ASO to target harmful huntingtin, called WVE-003. With less-than-encouraging results from the PRECISION-HD studies, why move forward with this third candidate?

Wave has learnt a lot from these trials and they think they can improve their chances for success with WVE-003. One key difference between WVE-003 and the earlier ASOs, WVE-120101 and WVE-120102, is the improved chemistry of this new ASO, which uses Wave's "next-generation PN backbone chemistry." Essentially this means there are changes to the ASO molecule structure which should hopefully make the drug perform better in patients. The upcoming trial of WVE-003 will test its safety and potency for huntingtin-lowering, similar to the PRECISION-HD1 and 2 trials.

The Phase 1b/2a clinical trial for WVE-003 will begin in 2021. Similar to other Wave ASOs, participants need a specific signature in their genetic code in order for the therapy to work, a tiny spelling difference between the healthy and expanded copies of the huntingtin gene, called a SNP. The SNP needed for WVE-003 treatment is found in 40 % of adults with HD, so all potential participants will need to be tested for the presence of this SNP before they can be enrolled in the trial. People who participated in the PRECISON-HD1 and 2 trials will be offered the opportunity to undergo SNP screening for potential enrolment in the WVE-003 trial.

How does this relate to the news from Roche last week?

Although the timing is extremely unfortunate, the Roche and Wave announcements are completely separate and not scientifically connected in any way. The PRECISION-HD trials had completed dosing, and Wave stated many months ago that the key results would be shared by the end of the first quarter of 2021. Dosing in the Roche GENERATION-HD1 trial came to an unexpected halt, and that news could not have affected Wave's timeline.

There's another important distinction between the two announcements: The results of the Wave studies showed that the WVE-120101 and WVE-120102 ASOs did not lower huntingtin protein in spinal fluid, even at the highest doses tested. Roche's drug tominersen DID lower levels of huntingtin in patients' spinal fluid in early trials, but development stopped based on findings midway through a longer and larger Phase 3 trial testing its effect on symptoms.

One possible reason that the PRECISION-HD trials struggled to lower huntingtin is that these ASO drugs used an older chemical structure. But the technology moves fast and is constantly improving, which is why there's hope that upcoming trials of WVE-003 could have a better outcome.

Onward once more

Although this has been a disappointing time for the HD community, this is by no means the end of the road for huntingtin lowering therapies. We still have very limited information about exactly why the (Roche trial)[https://en.hdbuzz.net/300] was halted, but details are forthcoming and will help to shape future trials. We'll learn from the PRECISION-HD trials, too, as the results are analyzed in greater depth and shared at upcoming scientific conferences and in future publications. There's still widespread evidence that targeting the HD gene at its source is a powerful approach, and there are many different ways that researchers and companies are exploring huntingtin-lowering: dozens of distinct drug designs, and multiple routes of delivery. There are also many additional therapeutic avenues that focus on other aspects of HD biology or aim to tackle a particular symptom.

The global HD community came together this week in an extraordinary way to seek support, share information, and talk about how to move forward, emotionally and scientifically. We continue to celebrate the heroes who participated in these trials and who are among the pioneers of huntingtin-lowering in people. We had all hoped for a better outcome for the PRECISION-HD trials, but we will move forward with a wealth of new knowledge. To quote Dr. Sarah Tabrizi of University College London in her comments to families about last week's news, "This is science, and science has to strive for the truth." We'll be here to report those truths as they arise.

Dr. Leora Fox works at the Huntington's Disease Society of America, which has relationships and non-disclosure agreements with pharmaceutical companies, including Wave Life Sciences and Roche. Rachel Harding declares no conflicts of interest. For more information about our disclosure policy see our FAQ...

GLOSSARY

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

huntingtin protein The protein produced by the HD gene.

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

placebo A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they’re taking a pill that doesn’t work.

single nucleotide polymorphisms a single-letter spelling difference in a gene. SNPs, pronounced 'snips', are common and most don't change the function of the gene.
