Sad news from Novartis: dosing suspended in VIBRANT-HD trial of branaplam

HDBuzz is saddened to share the news that the VIBRANT-HD trial of the oral huntingtin-lowering drug, branaplam, has been temporarily suspended for the safety of participants.

By Dr Leora Fox | **August 08, 2022** | **Edited by Dr Jeff Carroll**

The VIBRANT-HD study began in early 2022 and was a long-awaited trial of a huntingtin-lowering drug, branaplam, that could be taken by mouth. On Monday, August 8th, we learned that dosing has been temporarily suspended at the recommendation of an independent committee that is monitoring the data from the trial. This decision was made because of signs that some of the participants taking branaplam may be experiencing new problems with their nerves, known as peripheral neuropathy. Let's talk more about what happened and what's next.

The HD gene and the quest to lower huntingtin

Huntington's disease is genetic, meaning that it's passed down in families from generation to generation. The genetic mutation that causes HD occurs in a gene called huntingtin, which produces a faulty RNA recipe, ultimately producing an extra-long huntingtin protein. This protein is believed to be harmful to brain cells, causing them to become sick and eventually disappear, and this leads to the many different symptoms of HD.

Over the past decade or so, novel approaches to treating HD have focused on a technique called huntingtin-lowering, which aims to decrease the amount of harmful huntingtin protein in the brains of HD patients. So far, the ones tested in people have been pretty invasive, requiring frequent spinal injections or brain surgery to deliver. Novartis, however, had recently begun a clinical trial of a huntingtin-lowering drug that could be taken once weekly, by mouth.

Branaplam and the promise of oral huntingtin-lowering

The story of branaplam and the VIBRANT-HD trial began with a different disease, known as SMA, which affects children. SMA is also genetic; it causes worsening muscle weakness in

babies and young kids and is eventually fatal within just a few years.

Branaplam was originally developed as a genetic treatment for SMA. It is known as a splicing modulator - essentially this means that it can steer the remixing of theRNA recipe for the gene involved in SMA, and restore the function of the protein. In a fascinating twist of science, Novartis discovered that branaplam could also affect the RNA recipe for huntingtin, in this case leading to less huntingtin being produced.

In the summer of 2021, as more genetic treatment options became available for kids with SMA, Novartis made the decision to stop developing branaplam for kids with SMA, and to focus its efforts on adults with HD. This decision was supported by data in HD model animals, and very early safety trials of branaplam in healthy adults. Excitement built in the HD community around the possibility of an oral huntingtin-lowering treatment, and the Phase 2 VIBRANT-HD trial began in early 2022.

This week's sad news

The VIBRANT-HD trial was planned to involve 75 people with early symptoms of HD, at more than 20 sites around the world. The main goals of the study are to test safety and the ability of the drug to lower huntingtin measured in spinal fluid. The plan was to test high and low doses of branaplam, each taken as a liquid once weekly for four months. Since early 2022, only the first cohort of participants had begun the trial. This was approximately 25 people, around 20 taking low dose branaplam and 5 taking placebo.

We learned today that the dosing in the trial has been stopped for safety reasons. We'll get right to the point: branaplam was showing signs that it could be toxic to the nervous system. This was determined by an independent Data Monitoring Committee (DMC), a group of evaluators that has access to the data, long before the doctors, patients, or study sponsor (Novartis) know the outcomes. This is an important and standard practice in the vast majority of drug trials and it's exactly for this reason - to keep participants safe in the event that problems arise.

The recommendation to suspend dosing in the study was based specifically on signs that branaplam might be causing damage to nerves outside the brain and spinal cord, known as peripheral neuropathy. Evidence from neurological exams, nerve conduction studies, and assessments of HD symptoms, as well as measurements of levels of a protein called NfL in the blood, all pointed to some concerns that some patients could be experiencing new nerve damage in their limbs.

What happens next?

In the immediate term, everyone participating in the trial will stop taking the treatment they were assigned. However, they will be asked to continue having their planned study appointments, which include blood and spinal fluid collection, and tests of nerve health.

Essentially, the study will continue, but without branaplam or placebo, and participants will be monitored closely for other safety signs. This will be essential to understand as much as possible about branaplam's effects on adults with HD.

There may also have been some people who were all set to begin participating in the VIBRANT-HD trial, at either a low or a higher dose - these folks will not begin the study. Current participants and doctors will stay "blinded" until the end of the study, meaning they still don't know who was on drug or placebo.

What does this mean for branaplam...and huntingtin lowering?

Essentially, this trial suspension is a way to protect participants from further potential danger to their nervous systems. It also means that Novartis will need to take a step back, take the time to analyze and learn more from the data, and determine whether it would make sense to keep testing branaplam.

It might be that the drug is really not safe for people with HD, and moving forward isn't an option. On the other hand, it might be possible to use lower or less frequent dosing, or it could be that branaplam may have affected some participants differently than others. This latter possibility is similar to how Roche will be running a new trial of the huntingtin-lowering drug tominersen in a specific group of people.

It's a tremendous disappointment that branaplam looks much riskier than expected for adults with HD. This will of course be especially tough for the first brave trial participants in VIBRANT-HD. But the news affects everyone in the community who felt hopeful about the first oral huntingtin-lowering drug to be tested in people.

That said, this news is not reason to abandon hope in huntingtin-lowering - nor even in oral huntingtin lowering. Branaplam was originally designed to treat a different disease, and though it lowers huntingtin, there may be other reasons it is causing unforeseen issues, known as "off-target effects." There is another oral huntingtin-lowering drug in clinical trials right now – it's called PTC-518 and is being developed by PTC Therapeutics. Based on data published by the company, that drug may have more ideal drug properties, compared to branaplam. Importantly, PTC-518 shows more accumulation in the brain, compared to the rest of the body, and the brain is the primary treatment goal for HD. We look forward to updates from PTC after they digest the branaplam results, but we're hopeful that their trial can continue, if experts feel it's likely to be safe.

Gratitude and moving forward

Beyond these oral drugs, there's a wide field of folks working on various approaches to huntingtin lowering, and ongoing clinical trials are being conducted by uniQure and Wave, with Roche's next study in planning stages. There are also some important HD research

conferences approaching this summer and fall, and there is sure to be exciting news to share from HD clinical studies and basic research laboratories worldwide.

There's no doubt this is a tough day for the HD community, and for those of us hopeful for Huntingtin-lowering drugs to be an effective treatment for HD. But, as we often say, science is cumulative, and if we do it right, even failures in the clinic can teach us more than we knew before we started the trial.

The entire community owes the participants in the VIBRANT-HD study a huge debt. They rapidly signed up for the study, and their participation enabled us to get to this point – disappointing as it is – as quickly as possible. Their selfless contribution will enable the design of the next study to take into account the lessons learned in VIBRANT-HD, and get us closer to a day when we have effective treatments for HD.

Dr. Leora Fox works at the Huntington's Disease Society of America, which has relationships with the companies mentioned in this article, including Novartis. For more information about our disclosure policy see our FAQ...

GLOSSARY

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

therapeutics treatments

splicing the cutting up of RNA messages, to remove non-coding regions and join together coding regions.

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.

cohort a group of participants in a clinical research study

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
