Disappointing news from Novartis about branaplam and the VIBRANT-HD trial

Novartis have announced that they are ending development of the drug branaplam in Huntington's disease. Here, we review this latest news and its impact on the HD community.

By Dr Rachel Harding | December 09, 2022 | Edited by Dr Jeff Carroll

---

The pharmaceutical company Novartis has released a community update which announces that they are ending development of branaplam, a huntingtin lowering drug, for possible treatment in Huntington's disease (HD). This news comes following recent bad news about side effects of branaplam in HD patients, being tested in the VIBRANT-HD clinical trial, dosing of which was paused earlier this year. In this article we will break down this announcement and what this news means for the HD community.

Huntingtin-lowering therapies are being pursued in the clinic by many companies

Many companies are exploring huntingtin-lowering as a strategy for treating HD. HD is caused by a mutation in the huntingtin gene, which leads to the production of a faulty version of the huntingtin protein. The faulty protein causes all sorts of problems in the brain and including the death of nerve cells, which results in the symptoms of HD. Huntingtin-lowering drugs aim to reduce the levels of the faulty huntingtin protein in the brain , with a goal of slowing or stopping HD's progression.

Huntingtin-lowering treatments are being developed using a variety of different approaches, such as anti-sense oligonucleotides (Wave Life Science and Roche) or viral gene therapies (uniQure). One problem is that the drugs these companies have developed cannot easily spread through the whole body, so they are given to patients through an infusion into the spinal fluid, or by direct injection into the brain. Giving drugs this way is expensive and demanding for patients so this type of therapy could not be trivially rolled out to the global HD community.

To overcome these problems, researchers are keen to develop "small molecule therapies" which would be cheaper to manufacture and administer. Small molecule drugs can be formulated to be taken orally as a pill or syrup, like most common medicines you may

already be taking, such as pain killers or an allergy medication. Because they can hitch a ride in the bloodstream, small molecule drugs are also better at spreading to nearly all the organs of the body. Some small molecule drugs, although not all, can even make the leap from the blood into the brain – enabling treatment of the body and brain with a single drug.

Branaplam lowers huntingtin but was originally designed to treat another disease, SMA

Two different companies, Novartis and PTC Therapeutics, are both testing small molecule drugs which can lower huntingtin in HD patients. The drugs from both companies are called splice modulators because they target how our cells which edits genetic messages, a process call splicing. Each genetic message can be thought of like a story book, and when the story is over, the final part of the message reads the genetic equivalent of “the End” to tell the cell that the sequence for that message is complete. Splice modulator drugs rejig the pages of the story book so “The End” is read the ending, so the cell destroys the message and doesn’t make the associated protein at all. Just like you would toss a book that made no sense with a premature ending and read, “Once upon a time, The End”.

The splice modulator developed by Novartis is called branaplam, a drug originally developed for a completely different disease called spinal muscular atrophy (SMA), because it also changes the levels of a protein called SMN2, which underlies that disease. Very unexpectedly, scientists at Novartis discovered branaplam also changes the levels of the huntingtin protein in different models so wanted to explore if this drug might be a good treatment for people with HD in a trial called VIBRANT-HD.

Branaplam has bad side effects for some people treated with this drug

VIBRANT-HD aimed to work out if branaplam was safe and effective at lowering huntingtin levels but, before recruitment was completed, dosing for the trial was paused due to safety concerns. The decision to pause the trial was made by an independent Data Monitoring Committee, who assess data generated by the trial before the doctors, patients, or study sponsor (Novartis) know the outcomes to ensure participants are safe in case issues arise.

We have since learned in this most recent announcement that Novartis has decided to end all development of branaplam for HD due to safety concerns associated with the drug. When dosing was paused back in August, information was released indicating that there were issues in some study participants with a condition called peripheral neuropathy – damage to nerve cells outside of the brain and spinal cord. In this most recent announcement, Novartis have provided further information about safety issues seen in many, although not all, participants.

As we expected to learn, symptoms and changes in neurological examinations consistent with peripheral neuropathy were confirmed as being observed in some participants. Some participants also had increased levels of neurofilament light chain (NfL), a lab test used to assess injury or damage to nerve cells. This means that there may be damage to the nervous system after branaplam treatment. Also of concern is the observation that there was an increase in the size of a region of the brain called the ventricles. The ventricles are a fluid filled space deep in the brain and an increase in the size of this region can mean several different things, which we don't yet have enough information to fully understand. In their letter, Novartis state that no clinical symptoms have been associated with these brain scan findings to date.

What does this mean for HD patients who received branaplam?

Novartis have stated that all study participants who received branaplam will continue to be monitored. We don't yet know if the side effects experienced by participants in the trial are permanent or whether they will get better now that dosing with the drug is stopped, so monitoring of symptoms is important.

What can we learn from trials that end this way?

Trial failures like this can be very hard-hitting and it is very normal to feel upset about this type of news, especially for the brave and dedicated members of the HD community who participated in this trial. Despite this sad development, there is still a lot we can learn from trials which don't turn out as we had hoped. Tons of data is collected throughout the course of trials and more will continue to be collected in the coming months as things formally conclude. This data can give us important insights into what might have happened so that the community can learn and move on from this trial. Novartis has stated that they are committed to sharing what they learn with HD families, researchers, and other professionals in the HD community.

Do we know why branaplam didn't work as we had hoped?

This announcement is the latest in a series of disappointing news regarding HD trials so what's going on? It's important to note that branaplam was not developed to treat HD. We knew unexpected side effects were possible, because as well as lowering huntingtin, branaplam also changes the levels of the SMN2 protein, as well as potentially others. Changing the levels of lots of different proteins can disrupt the intricate processes performed by nerve cells, which could explain some of the symptoms observed.

In fact, in some animal studies, Novartis note in their announcement that toxicity of the nerves was seen as a side effect of branaplam treatment, which is why they included robust safety monitoring procedures in the VIBRANT-HD trial. Interestingly, children with SMA treated with branaplam do not seem to have these symptoms, which is why there was still optimism that this would not prove to be a problem in HD patients. We will likely learn more about why this happened as more data from the trial is compiled and analysed.

What does this mean for the other splice-modulator drugs to treat HD?

Other companies are working to develop a splice modulator to treat HD, including Roche who are doing pre-clinical research in this area. Another trial, called PIVOT-HD, will be testing the splice modulator PTC-518 developed by PTC therapeutics which is very similar to branaplam. This trial is underway in Europe and Australia although recruitment is paused in the US as PTC work to provide some extra data to the US regulatory agency, the FDA. It's important to note that PTC-518 was specifically designed for HD, and data from PTC indicates this drug spreads more efficiently into the brain than branaplam, so the hope is that the side effects observed for branaplam won't be an issue for PTC-518; we will learn more as the trial proceeds.

When will we learn more?

Novartis have vowed to keep the community updated as their analysis of the data from the trial proceeds. HDBuzz will write another article as soon as we learn any more information about branaplam or the VIBRANT-HD trial.

It's important to remember clinical trials are some of the biggest and most complicated experiments which we can run, with no guarantees of good outcomes, but each trial adds to our knowledge and brings us closer to finding drugs to treat HD. We are extremely grateful to the brave and selfless HD community members who participated in this trial.

The authors have no conflicts to declare. 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

ventricle Normal fluid-filled spaces within the brain.

anti-sense the half of the DNA double-helix that is mostly used as a backup, but sometimes produces message molecules

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