No pivot needed for PTC-518

PTC Therapeutics shared 12 month data from the PIVOT-HD trial, testing the oral HTT lowering drug PTC-518. While designed to assess safety, they shared encouraging results that the drug showed promising signs for biomarkers and some clinical metrics.

 **By Dr Sarah Hernandez** | **June 21, 2024** | **Edited by Dr Rachel Harding**

On June 20, 2024, we received an update from PTC Therapeutics about their ongoing trial, PIVOT-HD. PIVOT is testing PTC-518, a small molecule drug, taken as a pill, that lowers huntingtin (HTT) in people with Huntington's disease (HD). Their most recent update shared data from people who had been on the drug for 12 months. Read on to learn what their new results tell us!

HTT lowering

Before we get into the juicy details of the data release, let's cover some basics about why PTC is interested in lowering HTT and what they hope it will do.

PTC-518 is something called a splice modulator - it works to lower HTT by rearranging the genetic message. By putting "The End" to the middle of the story, the message no longer makes sense and the cell doesn't produce the HTT protein.

We know that the genetic cause of HD is an expansion of the genetic code within the *HTT* gene. There's an extra bit of genetic message that repeats the letters C, A, and G more times than it should. When someone has 40 or more CAG repeats in their HTT gene, they'll go on to develop HD, unless researchers can find some way to intervene.

With such a conclusive test for determining if someone will develop HD, researchers have narrowed in on the HTT gene itself to develop potential treatments. We now have the technology to target HTT and reduce the amount of protein that's produced. The thought is, with less of this nefarious player, progression of the disease itself would be slowed, or possibly stopped. Lowering HTT in the lab in animal models of HD has had success, and it's now being tested in people.

PTC's approach for lowering HTT

There are several companies testing HTT lowering in trials, and many of them are taking different approaches. We've covered ongoing HTT lowering trials from Roche, uniQure, and Wave Therapeutics. Currently, PTC Therapeutics is one of two companies testing a pill that can lower HTT in clinical trials. (The other is Skyhawk Therapeutics, who are advancing their HTT lowering small molecule SKY-0515.) PTC's drug, PTC-518, works by rearranging the HTT message molecule.

Like stories, all genetic messages have a beginning, a middle, and an end. The end is the part of the code that tells molecules that the genetic story is over, like the last page in a storybook that reads, "The End". PTC-518 works placing "The End" into the middle of the message. So rather than a logical story, the message is interrupted by "The End". The cell realizes that the message doesn't make any sense, and doesn't bother making that protein.

After encouraging results in animal studies, PTC Therapeutics moved their drug into clinical trials. PIVOT-HD is a Phase 2 trial primarily designed to test the safety and tolerability of PTC-518. It tests 2 doses (5 mg and 10 mg) over the course of 12 months in people in Stage 2 and early Stage 3 of HD according to the HD-ISS.These are people who have begun to show clinical signs of HD and have just started showing difficulties with daily functioning. After the 12 months, all participants can continue taking the drug in an open label extension.

PIVOT-HD is a very small and relatively short trial, with just 32 people enrolled for the 12 month study - we don't want to give too many folks the drug for too long until we know for sure it is safe. Although safety is one of the key goals of the study, lots of other measurements are taken to see how the drug might be working. These provide exciting hints but we really need a Phase 3 trial, which would test the drug in a lot more people for a longer timeframe, to see whether PTC-518 actually slows or halts HD.

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What we learned a year ago

The last update we received about PTC-518 was exactly a year ago. That update released 12 week data from people with HD taking PTC-518. In the summer of 2023 we learned that PTC-518 did seem to lower HTT levels in blood. This may seem like an obvious point, but checking that the drug working as expected is important so that we know things are on the

right track.

We also learned that PTC-518 was well tolerated overall, it got to the brain, andbiomarker levels seemed to remain stable over the 12 week timeframe. The specific biomarker that was measured was neurofilament light (NfL), which measures the breakdown of brain cells, and is used as a measure of overall brain health. NfL steadily increases in people with HD as the disease progresses. NfL is becoming one of the field's most reliable biomarkers to track HD progression. Last year's data release suggested that PTC-518 seemed to be on the right path, so the study continued.

12 months later - biomarkers moving in the right direction!

People in the PIVOT-HD trial have now been taking PTC-518 for 12 months. The key objectives for the 12 month time point are to: 1) show that the drug is still getting to the brain and lowering HTT, 2) examine disease biomarkers, and 3) measure any changes in participant functionality. Cutting to the chase - things look positive for all of their 12 month objectives!

To determine if PTC-518 is lowering HTT in the brain, they take a sample of the cerebrospinal fluid (CSF) that bathes the brain. Since they can't directly sample brain cells, this is the next best option to measure what's going on with HTT levels in the brain. PTC reported that 5 mg of PTC-518 lowers HTT in the CSF by ~20%, and 10 mg by ~40%. Similar decreases were also seen in blood samples taken.

At 12 months, one of the biomarkers that they examined was NfL levels in blood. Natural history studies, like Enroll-HD, have shown us that NfL levels in blood typically increase by about 10-12% per year in people with Stage 2 HD.

The 12 month data release from PTC Therapeutics is GOOD news! PTC-518 seems to be following trends that could suggest that it may lead to improvements in biomarkers of brain health and clinical metrics of daily functioning. This is fantastic news for a community thirsty for a tall glass of good news!

In people taking PTC-518 for 12 months, the increase seemed to slow down and was 3% on 5 mg of PTC-518 and 4% in people taking 10 mg. These results show that taking PTC-518 does not seem to cause the brain any harm, and in fact, may even slow the damage to brain cells that occurs in HD.

12 months later - improved clinical scores!

For clinical metrics to determine how PTC-518 affects functionality of people with HD, they examined Total Motor Score (TMS), the Composite Unified Huntington's Disease Rating Scale (cUHDRS), and Total Functional Capacity (TFC). What a mouthful! Let's break down what they found.

The TMS scale measures movement symptoms in people with HD. For people taking PTC-518, there was a reduced progression on the TMS by over 70%! In the webcast update, PTC Therapeutics noted that the TMS is one of the most reliable metrics for determining disease progression in people with Stage 2 HD. So reducing progression of TMS is very encouraging as it suggests there might be a slowing of disease progression.

The cUHDRS is one of the most comprehensive clinical measures for assessing HD progression. It looks at changes in movement, thinking, behavior, and functioning. Typically, people with HD progress by 1 point on this scale per year. In people taking PTC-518, this progression seems to be cut in about half.

TFC measures the ability of a person to function on day-to-day tasks and looks at the ability of someone to hold a job, do their own finances, and carry out activities of daily living. In people taking PTC-518, this also looks to have moved in a positive direction. Together, these improvements in clinical scores suggest that taking PTC-518 could have a chance at slowing the progression of HD - very big news!

FDA hold lifted

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While the most exciting updates were related to biomarkers and clinical scores (understandably!), PTC also looked at safety. At the end of the day, this Phase 2 trial is ultimately designed to test the safety and tolerability of PTC-518. Thankfully, all safety metrics suggest that PTC-518 is also checking this box. The most common symptoms reported were headache, falls, and flu-like symptoms, which were also reported in the placebo group.

Another important note, especially for the very astute readers, is that the FDA has lifted their hold on PTC-518. We previously reported that the FDA was pausing the PTC-518 clinical trial in the U.S. This wasn't related to the safety of the drug, but rather the amount of data that had been produced to that point and shared with the FDA. The regulatory agency likes to see animal data extending past the time point being tested in the trial in people, and PTC only had data out to 3 months at that point. Excitingly, the new 12 month data has convinced the FDA to lift their previous hold in the U.S.

What's next for PTC-518?

Overall, this is GOOD news! And we realize the HD community is very thirsty for a tall glass of good news at this point. However, we do need to temper expectations on all this excitement a bit. While these results are encouraging, they can't be used to conclusively say if PTC-518 will be effective in modifying disease course of HD.

The ultimate goal of this Phase 2 trial is to work out if PTC-518 is safe enough to move into a larger Phase 3 study. The number of people in the trial is very small, at a total of 32 participants, so any conclusions drawn about the biomarker and clinical data need to be taken with a pinch of salt.

To conclusively determine if PTC-518 is effective in treating HD, a Phase 3 trial will need to be performed. Thankfully, PTC announced in their update that they're in the midst of planning that Phase 3 trial. This trial will specifically be designed to test how well PTC-518 works in slowing or stopping progression of HD. They hope that this trial will serve to land them close to regulatory approval in what would be the first ever disease modifying treatment for HD, a drug for which we're all eagerly waiting!

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

Total Functional Capacity A standardized rating scale for function in HD, used to assess capacity to work, handle finances, perform domestic chores and self-care tasks

CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

NfL biomarker of brain health

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

therapeutics treatments

open label A trial in which the patient and doctor know what drug is being used. Open label trials are susceptible to bias through placebo effects.

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

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.

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15
