Disappointing news from LEGATO-HD trial of laquinimod in Huntington's disease

The LEGATO-HD trial of laquinimod did not slow progression of Huntington's disease. Here's the lowdown.

By Dr Jeff Carroll | August 02, 2018 | Edited by Professor Ed Wild

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The LEGATO-HD trial of laquinimod to slow progression of Huntington's disease did not meet its primary endpoint. What's an endpoint, and what does this all mean for HD families?

What was the Legato-HD trial all about?

The Legato-HD trial was designed to test whether treatment with a drug called**Laquinimod** could slow the progression of Huntington's Disease symptoms. The drug is being developed by Active Biotech in partnership with Israeli drug company Teva Pharmaceuticals, who are testing whether the drug is beneficial in two brain diseases - Multiple Sclerosis (MS) and HD.

The aim of the trial was to see whether damping down the immune system in the brain slowed progression of HD.

In both MS and HD, the immune system is hyper-activated, particularly in the brain. InMS, there are very clear links between this hyper-activation of the immune system and symptoms. In HD, the link is a little less obvious, but HD patients and some animal models of the disease show signs of increased brain immune system activation.

Teva tested Laquinimod in HD patients in partnership with the Huntington Study Group and the European Huntington's Disease Network in a trial called **Legato-HD**. This trial enrolled 351 HD patients across the world, and gave them one of three doses of Laquinimod, or a placebo treatment.

There was a bit of a hiccup part-way through the trial - based on concerns raised in anMS trial about high doses of Laquinimod, the highest of three doses being tested was dropped from the Legato-HD study in 2016. Unfortunately that reduced the number of people taking the drug, as well as the average dose in treated patients, which inevitably reduced the chance of a positive result.

A word on endpoints

Before we talk about the findings, a reminder - a critical part of designing a trial is picking an **endpoint**, or the specific change you want your drug to make in people taking it. One of the ways we protect ourselves from wishful thinking in science is to have a requirement that researchers testing drugs define what they hope their drug will do up front, rather than after they've done a trial.

Once researchers have defined what change they want to see, this becomes the so-called **primary endpoint** of the study. If the trial shows that theprimary endpoint was met, meaning the hoped-for change was observed, the result is considered positive. If not, the trial is considered negative, even if other symptoms or aspects of the disease are improved.

Although there is generally only one endpoint for a trial, drug companies often establish **secondary endpoints** when they set up a trial. These are aspects of the disease that researchers hope might improve, but won't define success or failure for the study. Unlike the primary endpoint, people who run trials often establish many secondary endpoints, because it's useful to look at trial volunteers as deeply as possible during the study.

What were the Legato-HD endpoints?

So, what were the endpoints that were pre-defined for the Legato-HD study? The researchers running the trial selected a score that measures how a trial particpant moves. This *total motor score* includes both problems with extra movements common in HD, as well as trouble with normal movements like walking and eye movements. The primary endpoint, or goal, of the Legato-HD study was to slow the worsening of this total motor score when examined 12 months after starting treatment.

The researchers running the Legato-HD study also stipulated four secondary endpoints. Recall, these are aspects of HD that the researchers were hoping would benefit from Laquinimod treatment, but that are not going to be used to determine whether the trial is formally a success - only the primary endpoint can do that.

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> **do, which is to tell us whether Laquinimod treatment helps with the movement symptoms of HD ”**

For the Legato-HD study, the secondary endpoints included a measurement of the volume of specific brain structure which shrinks during the course of HD. They also included three other measurements of disease progression.

What do we know?

On July 31st, the Legato-HD trial sponsors put out a press release with a summary of the key findings from the Legato-HD study. This is common with these sorts of trials - trial sponsors initially put out a pretty basic press release with the key findings, and then later publish a deeper set of findings in a published study.

Unfortunately, the press release states that Laquinimod: “did not meet its primary endpoint of change from baseline after 12 months of treatment”. This means that the movement scale that was chosen as the primary endpoint for the study did now show sufficient improvement in HD patients taking Laquinimod to prove to the investigators that the drug was working.

However, the press release continues: “The study’s secondary endpoint, reduction of brain atrophy … was met”. This could be quite interesting, as it suggests the drug might be having some effect on the underlying disease process, which is accompanied with shrinkage of the brain. However, it’s likely that the other three secondary endpoints were **not** met, or they would have been mentioned in the press release.

Caution is warranted here. There is a long history of secondary endpoints looking positive in an initial study, and then not being seen again when tested subsequently. So while we’re excited about the potential impact of Launimod treatment of brain volume in HD, we have to reserve judgement until we see the results.

Is this a failed trial?

It’s disappointing that the Legato-HD study did not meet its primary endpoint, but we don’t consider that this is a “failure”. The trial is a success because it succeeded in doing what it was designed to do, which is to tell us whether Laquinimod treatment helps with the movement symptoms of HD. It doesn’t, and now we know and can move on to the next set of experiments and ideas for HD treatments.

We often say that science is cumulative, and today we learned something new about what works, and doesn’t work, in HD - that’s progress!

Ed Wild, who edited this piece, was a site investigator on the LEGATO-HD trial. His institution (University College London Hospitals) received payment for participating, but Ed did not. He has no financial interest in the outcome of the trial. For more information about

our disclosure policy see our FAQ...

GLOSSARY

secondary endpoints Additional questions asked in a clinical trial that help scientists look at treated patients as broadly as they can to determine the effects of a drug

multiple sclerosis a disease of the brain and spinal cord, in which episodes of inflammation cause damage. Unlike Huntington's disease, MS isn't genetically inherited.

primary endpoint The main question asked in a clinical trial

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.

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