Sad news from the SIGNAL study: pepinemab does not influence HD symptoms

The SIGNAL study did not meet its key clinical goals for #HuntingtonsDisease to slow or improve HD symptoms, but the results are still informative for the HD community and other fields.

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The SIGNAL clinical trial was designed to test a drug called pepinemab in people with early Huntington's disease. The key results of that trial were recently announced, and unfortunately, pepinemab did not slow or improve HD symptoms as hoped.

What was the SIGNAL trial, and who participated?

The SIGNAL trial was launched in 2015 by a company called Vaccinex. It was designed to test whether a drug called pepinemab (also known as VX15) was safe for people with HD, and whether it could slow the effects of HD, like changes to the brain, and difficulties with thinking, movements, and behavior. Key results from the trial were announced recently, and the bottom line is that pepinemab did not benefit people with HD.

When planning an HD trial, investigators must decide upon key clinical goals called "primary endpoints," which are chosen based on laboratory data, expert medical and statistical opinions, and input from HD families.

Image credit: Joseph Mucira

The 301 trial participants were all HD gene carriers, some of whom had begun to experience chorea, the typical movement symptoms of HD, and some who had not yet. The period just before the onset of chorea is sometimes called the "late prodromal " stage of HD, and the period when a person is beginning to experience chorea is often called the "early manifest" stage.

HD trials often select people with “early manifest HD,” those with subtle movement symptoms, because this is historically when an HD diagnosis is made, but also because it’s a time when changes in symptoms and the speed they develop can be measured most reliably. We are indebted to the participants in this trial, who took a brave and generous risk. The trial results, although disappointing, will provide invaluable information about HD progression and about pepinemab, which is now being tested in Alzheimer’s patients, as well as in some forms of cancer.

What happened during the trial?

There were two main groups of people in the trial, referred to as “Cohort A” and “Cohort B”. The people in Group A began and ended the trial first, and participated for a shorter period. Group B was larger, and those participants had a longer period of monitoring and a slightly different series of treatments. The results from Group A were shared in 2018, when an analysis of brain imaging done by the company suggested that pepinemab might be slowing brain shrinkage in HD. Vaccinex most recently shared the results from Cohort B, which were unfortunately disappointing.

In general, everyone in the trial visited study sites every month for a year to receive an intravenous (IV) drip. Half of participants received pepinemab, and half got a placebo, a saline solution with no drug (essentially some extra fluids). Many of the visits included tests and procedures, like MRI imaging, learning and memory activities, physical exams, and blood draws. To prevent any bias during these visits, neither the participants nor the doctors knew who was getting pepinemab and who was getting placebo. This is known as a double-blind clinical trial, and it is the gold standard for testing drugs in people.

After the first year, participants continued to come in for visits for an additional 6 months or up to two years, to monitor their health, safety, and abilities during and after the trial. Then, statisticians analyzed the data and Vaccinex shared the results with the community.

Planning a clinical trial

To put the SIGNAL trial results into context, it is first helpful to retrace the steps back to the planning stages of an HD clinical trial, which is a long, hard road. Pharmaceutical companies must take into account their laboratory data (testing in cells and animals), as well as the advice of many people in the field, including doctors and researchers specializing in HD, statisticians, and the true experts, HD families. Then, the investigators decide upon key clinical goals, known as “primary endpoints.” These are the most important measurements that will be taken during the trial, and they are used later to decide whether the drug has successfully treated participants with HD.

Depending on the drug and the trial goals, this might be measurements of a person’s movement patterns, their levels of anxiety and depression, or even reports of day-to-day function from the patient and their loved ones. Before the trial begins, the investigators must apply to regulatory agencies like the FDA in the USA and the EMA in Europe, to explain why they have chosen their primary endpoints, what exactly trial participation involves, and how they will analyze their data.

If a drug does not work to improve the key symptoms or measurements decided upon at the beginning, the trial is said to have “failed to meet the primary endpoints.” Unfortunately, this is exactly what happened for the SIGNAL trial.

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What were the results of the SIGNAL trial?

In addition to measuring the safety and side effects of pepinemab, the SIGNAL study had two primary endpoints related to the HD participants’ thinking abilities and general well-being. The first was a set of cognitive tests to measure memory, planning, and ability to follow instructions. The second was an evaluation made by the study doctors to summarize how each participant was doing over the course of the trial, taking into account their health, behavior, and ability to function day-to-day.

At the end of the SIGNAL trial, pepinemab was deemed safe and tolerable (not too many serious side effects). However, participants who received the drug did not perform better than those who received the placebo, on either the cognitive tests or the doctor’s assessment. Because the trial did not achieve its clinical goals, many news sources have deemed the SIGNAL study a “failure.” It’s true that the study failed in that it did not meet the primary endpoints.

However, some reports have stated that pepinemab may still “support potential for cognitive benefit,” suggesting that it still holds promise. That’s because the group of HD patients that received pepinemab may have had slight improvements on some tasks used to test thinking and organization skills, like planning sequences to move objects from one configuration into another, or keeping pace with tapping their fingers at changing speeds. These improvements did not reach “statistical significance,” which means that there was no mathematical difference between the placebo and drug groups – no definite improvements from treatment with pepinemab. When the math is very close, it’s sometimes said that there is a “trend towards benefit,” which is a bit like saying that the trial was *almost* successful. That’s frustrating for the entire HD community.

What can we learn from a “failed” trial?

So - could pepinemab still benefit a different group of people with HD, or with another disease? Maybe. Perhaps if the trial had tested more people, had been designed with a different primary endpoint, or had focused on people who had greater impairments in thinking to begin with, the outcome would have been different. The problem with expounding on these “ifs,” of course, is that HD patients need treatments that are proven to be helpful, not almost-helpful. An HD treatment that is significantly, mathematically, clinically helpful will improve performance on study tests, make symptoms easier to manage, or slow down the course of HD.

Potential benefits of pepinemab did not reach statistical significance, which means that there was no mathematical difference between the placebo and drug groups – no definite improvements from treatment.

Image credit: Gerd Altmann

The actual target of pepinemab in the body is a type of receptor that receives messages from a molecule called semaphorin 4D (SEMA4D). SEMA4D oversees parts of the inflammatory response meant to fight intruders and clean up around cells, but overactive inflammatory responses are a problem in many brain diseases and cancers. Because SEMA4D's role is not specific to Huntington's disease, some HD researchers and clinicians were skeptical of the decision to test it in HD patients. But the hope was that blocking SEMA4D with pepinemab in HD patients would reduce inflammation in the brain, preserve the health and growth of brain cells, and help with symptoms.

Pepinemab did not show a benefit for people with HD in the SIGNAL study – the primary endpoints were not met. This is why so many news sources are reporting the trial as a "failure." However, this does not mean that the trial was a waste of time, or that the participants' efforts were for naught. All good clinical trials are designed to give us more information about the drug and the disease, regardless of whether the treatment succeeds. In fact, blood samples and years of data carefully collected during study visits are invaluable to our understanding of HD progression, and the results of the SIGNAL trial will inform trials of pepinemab in Alzheimer's and Head and Neck Cancer patients.

What's next?

It is possible that targeting SEMA4D could benefit dementia patients, who experience a different kind of memory impairment, or cancer patients, who have a different problem with inflammation. Well-designed clinical trials will tell us whether this is the case; SIGNAL-AD has recently begun recruiting people with Alzheimer's disease. Vaccinex has suggested that another trial of pepinemab in HD patients may be warranted, one that is larger or specific to those with more advanced cognitive difficulties, but it's not likely in the near future.

There is fortunately a rich and active HD research pipeline, with genetic therapies addressing the direct source of the disease, and other treatments targeting a range of HD-specific symptoms. We look back on every "failed" study with gratitude towards those who have made new knowledge about HD treatments possible, and we look forward to the results of ongoing and future trials.

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

GLOSSARY

primary endpoint The main question asked in a clinical trial

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

inflammation Activation of the immune system, thought to be involved in the HD disease process

prodromal prior to onset or diagnosis of movement symptoms

Receptor a molecule on the surface of a cell that signalling chemicals attach to

manifest after HD diagnosis, or when symptoms are already showing

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.

chorea Involuntary, irregular 'fidgety' movements that are common in HD

cohort a group of participants in a clinical research study

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

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