SURVEYOR opens the door for drugs that treat cognition

Sage Therapeutics announced results from SURVEYOR, a trial that looked at cognitive changes in people with HD, and tested short-term safety of dalzanemdor. The study was small but met key goals, and additional trials are in progress.

By Dr Leora Fox | June 12, 2024 | Edited by Dr Sarah Hernandez

---

Sage Therapeutics released a press statement on June 11th that focuses on the main results of a study called SURVEYOR, aimed at studying cognition (thinking) in Huntinton's disease (HD) and testing the safety of a drug called dalzanemdor (previously SAGE-718). Let's talk about what we know and what's next!

Amplifying nerve cell messages to improve thinking

Sage Therapeutics works on brain health across a variety of diseases. One of their areas of focus is cognition (thinking) and executive function - the ability to make decisions, plan, and act on new information. This area of research is particularly relevant to the HD field, because cognitive changes have a huge impact for people living with HD.

Dalzanemdor is like giving your brain cells a megaphone. It works by turning up the volume of the molecular messages being passed by NMDA receptors, which are typically reduced in HD and cause issues with thinking and memory.

Sage has been working on an experimental therapy called dalzanemdor. The drug acts on NMDA receptors, which help to transmit chemical messages between nerve cells. There is an imbalance in this messenger system across many diseases, which causes changes in

thinking and memory. Dalzanemdor is a type of drug designed to boost the messages passed by NMDA receptors - it's a bit like giving your brain cells a megaphone.

Sage has applied this approach to HD, but also to diseases like Parkinson's and Alzheimer's, which also involve changes in executive function over time.

Treating the cognitive symptoms of HD

There are some challenges when developing drugs to treat the cognitive symptoms of HD. Since HD was traditionally defined as a movement disorder, and is still officially diagnosed once movement symptoms develop, clinical trials have historically been designed to show changes in movement symptoms.

Our understanding of HD has evolved more recently through important observational studies like PREDICT-HD, TRACK-HD, and Enroll-HD. Clinical researchers are also developing new tools to better measure subtle changes in thinking symptoms, and scientists are developing new biomarkers to follow changes over time and responses to drugs. This has led to a shift in how informed families, scientists, and medical professionals think about HD, but systemic change happens more slowly.

Newer types of cognitive tests can show that cognitive changes are happening over time in a measurable way in people with HD. One group of tests, developed about a decade ago, is called the Huntington's disease cognitive assessment battery (HD-CAB). It involves separate tests around problem solving, matching, language, and other aspects of thought and executive function. More data in this realm will ultimately help to convince regulatory agencies (those that approve drugs, like the FDA in the U.S. and EMA in Europe), that a new treatment can move the needle for people with HD, especially when it comes to early changes in thinking.

> **"Newer types of cognitive tests can show that cognitive changes are happening over time in a measurable way in people with HD. "**

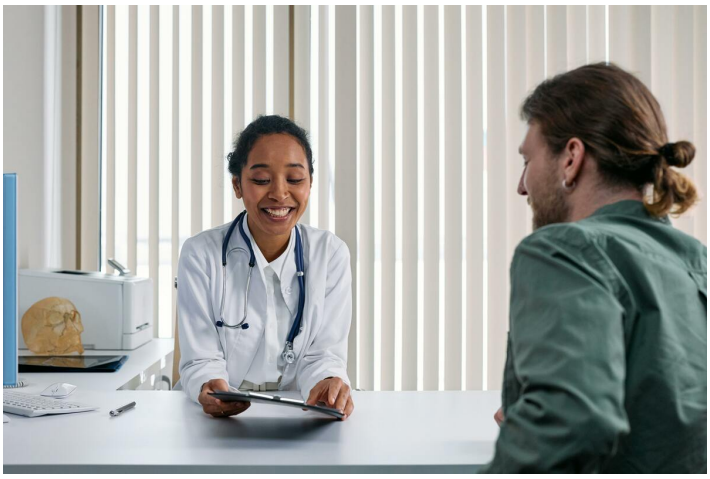
The PERSPECTIVE Program and the SURVEYOR trial

Previously, Sage has conducted a number of (small) trials of dalzanemdor in healthy volunteers, people with HD, and people with Parkinson's and Alzheimer's. Currently, they are working on a series of trials that are designed both to confirm cognitive changes in HD and test the safety of their experimental therapy, dalzanemdor. The overall program is called PERSPECTIVE. It involves the following:

- The SURVEYOR study, a small, 28-day study to look at cognitive changes and safety.

- The DIMENSION study, a larger, 3-month study to look more closely at the safety of dalzanemdor and how the body processes the drug, as well as its potential impact on cognitive symptoms of HD.
- The PURVIEW study, a longer study known as an open-label extension, in which everyone involved receives the drug. Participants with HD in SURVEYOR and DIMENSION could choose to join this study and continue receiving dalzanemdor.

Recent news from the SURVEYOR study



SURVEYOR used various tests to objectively measure thinking changes that occur in people with HD. Having data to support that these cognitive changes happen during the disease opens the door for designing drugs to improve these symptoms.

The SURVEYOR study is the focus of the June 11th 2024 press release. The main goals of the study were to measure cognitive impairment in HD compared to healthy participants and to look at the safety of dalzanemdor in participants with HD. Sage also wanted to better understand the relationship between changes in thinking and changes in function in people with HD.

The study involved 40 people with HD and 29 people who did not have HD. The first step was to have all the participants take the HD-CAB cognitive tests, and compare those with and without HD. Next, those with HD were divided into two groups. One group took dalzanemdor (a daily pill) for 28 days, and the other took a placebo (a sugar pill). Before, during, and after the drug period and up to a few weeks later, the participants completed the HD-CAB again, had other physical and safety tests, and reported on side effects.

The press release from Sage shared a couple of key pieces of information about the trial:

1. The HD-CAB tests confirmed cognitive changes between people with and without HD. This is important because it will help advance trial metrics beyond those that currently focus on movements associated with HD, like chorea. Objective evidence for the impact that HD has on cognitive changes shows that these metrics can be used in a meaningful way for larger clinical trials.

2. Dalzanemdor overall appears to be safe and well tolerated. While some participants reported “mild to moderate” side effects because of the drug, no one left the trial because of those effects. However, we don’t yet know what those effects were. Additionally, there were no new safety issues reported. This is good news considering that dalzanemdor has been given to many people across several clinical trials.
3. There may have been a slight improvement in cognition for people on dalzanemdor, compared to those on placebo, as measured by some individual tests within the HD-CAB. However, it’s important to note that this short study wasn’t designed to test this, so no conclusions can be drawn at this time about the ability of dalzanemdor to treat HD symptoms. Sage will look more closely at the data to understand what this means, but the preliminary results support moving forward with the program.

> **“Overall, Sage’s recent press release about the SURVEYOR trial suggests dalzanemdor is generally safe. And perhaps more importantly, it suggests we have a robust way to measure cognition in HD with the HD-CAB. ”**

More to come for dalzanemdor

Overall, Sage’s recent press release about the SURVEYOR trial suggests dalzanemdor is generally safe. And perhaps more importantly, it suggests we have a robust way to measure cognition in HD with the HD-CAB. This piece will be critical for moving drugs forward that are designed to treat cognitive issues associated with HD.

Sage recently shared at the 2024 HDSA Convention that recruitment for their PURVIEW open label extension study is ongoing. The DIMENSION study is still ongoing, though no longer recruiting, but Sage is expected to release data associated with that trial by the end of the year. Since this larger trial is specifically designed to test the ability of dalzanemdor to treat cognition in HD, we should have a good idea by the time we reach 2025 if dalzanemdor is effective for HD. Stay tuned!

Leora Fox works at the Huntington's Disease Society of America, which has relationships and nondisclosure agreements with some pharmaceutical companies studying HD, including Sage Therapeutics. For more information about our disclosure policy see our FAQ...

GLOSSARY

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

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.

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
