The dust has settled: Sage's dalzanemdor won't advance for cognitive impairment

Changes in thinking, learning, and memory are some of the most distressing and impactful in Huntington's disease. Sage Therapeutics was advancing their drug dalzanemdor to treat these symptoms, but unfortunately this program will be halted.

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The Huntington's disease (HD) community received the news on November 20, 2024 that Sage Therapeutics would be halting the development of their drug dalzanemdor (previously SAGE-718) for HD. Sage had hoped that dalzenemdor would work to improve thinking problems experienced by people with HD and had recent setbacks with the same drug for other diseases. There's no other way to say it: this is disappointing news and many people will feel disheartened today. Let's break down what we learned from Sage in their recent press release and what this means for the HD community.

Thinking and memory in Huntington's

HD is classically thought of as a movement disorder and onset is still often clinically defined as when these motor symptoms begin. However, HD causes many other effects, such as changes in cognition (thinking, learning, and memory).

Huntington's Disease (HD) causes changes in how people think, learn, and remember. These symptoms can have a serious impact on quality of life for people with HD.

Newer types of tests can measure cognitive changes in people with HD. The Huntington's disease cognitive assessment battery (HD-CAB) was developed about a decade ago specifically to look at changes in thinking, learning, and memory in people with HD. This is a

set of tests that measures things like problem solving, matching, language, and other aspects of thought and executive function.

These new tests show that the cognitive changes that happen over time as HD progresses can be measured. With that, it has allowed drug developers to target thinking, learning, and memory, with the hopes of developing drugs to improve these cognitive symptoms. Medications targeted at cognitive changes could have a massive benefit for people with HD, such as helping them to maintain work performance and keep their jobs longer, which could expand working years for some people to defray the financial burden of HD.

Turning up the volume on thinking

Sage Therapeutics has focused on developing drugs to help treat cognition. Not just for HD, but for other diseases, like Parkinson's and Alzheimer's, where cognitive changes also occur.

Their drug dalzanemdor works by amplifying molecular messages in the brain. These molecular messages help brain cells communicate and work to try and improve cognitive function. In diseases like HD, these molecular messages are lower. The hope is that by turning up the volume on these molecular messages, thinking, learning, and memory will improve

Dalzanemdor trials

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Sage began running several trials to test the ability of dalzanemdor to improve cognitive impairment for various diseases, including Parkison's, Alzheimer's, and HD.

Unfortunately, they announced in April of 2024 that, while dalzanemdor was generally safe and well tolerated, the trial did not meet the clinical endpoints for Parkinson's disease. The trial showed that people taking dalzanemdor did not have meaningful differences in thinking tests compared to those on a sugar pill. Then in October of 2024 there was a similar announcement for their trial testing dalzanemdor for Alzheimer's disease.

The Phase 2 DIMENSION study in HD was the last major trial to see if dalzanemdor could improve problems with thinking, learning, and memory for people who had a disease that causes cognitive problems. Unfortunately, we learned today, that the outcome for dalzanemdor for HD was similar to the previous trials

DIMENSION

The DIMENSION study was a 12-week clinical trial testing the effects of dalzanemdor on cognitive function in people with HD. There were 189 people that were randomly assigned to either take the drug or a sugar pill. Overall, dalzanemdor was generally safe and well tolerated.

In the study, cognitive function was measured with various tests, like the Symbol Digit Modality Test (SDMT). In this test, people are essentially asked to break a code - numbers are assigned to abstract symbols and people are asked to read out the numerical code associated with a string of symbols. This test measures various components of cognition, such as attention, visual processing, working memory, and thinking speed.

Even when clinical trials don't get us the results we hope for, there is still a lot we can learn from all of the data collected. This can help scientists design better drugs in the future to treat Huntington's disease.

Unfortunately, those taking dalzanemdor didn't show any cognitive improvements when compared to the group taking the sugar pill. Overall, DIMENSION failed to meet the clinical endpoints of the trial. Because of this, Sage has decided to halt the trial and future development of dalzanemdor. This includes halting the PURVIEW Study, which was an open label extension of their previous SURVEYOR Study, a small 28-day trial testing dalzanemdor in HD.

No trial is a failure

Trials may fail to meet their clinical endpoints, but no trial is a failure. There's always something to be learned. From dalzanemdor, there are three main takeaways:

Firstly, the HD community is eager to have drugs that could improve cognitive changes. A recent meeting with the US Food and Drug Administration (FDA) hosted by the Huntington's Disease Society of America (HDSA) made that clear. This all-day event gave HD families a platform to share the effects and daily impacts of HD with the US regulatory agency responsible for approving HD drugs. What was clear from this meeting is that HD families want drugs to help with cognitive symptoms caused by HD.

Secondly, trials like DIMENSION collect a huge amount of data from a large number of

people. These rich datasets and the findings of the trial can help researchers better understand different aspects of HD. Specifically, this kind of data can help to better pinpoint how HD changes cognition over time, and give insights into how drugs might be better designed in the future.

Thirdly, we now know that running clinical trials that test the ability of drugs to change cognitive symptoms is possible. The advent of tests like the HD-CAB and SDMT, along with their use in clinical trials like DIMENSION, show that we can objectively measure these changes in people with HD. Now it's up to the drug developers to use this information and continue to advance drugs for cognitive changes in HD.

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Dusting ourselves off

Sometimes bad news is just that, bad. There's no doubt that this news will come as a massive disappointment to many people in the trial that felt they were gaining something from dalzanemdor. It's ok to be upset about this, but try to not let yourself get stuck there.

There's a lot of *good* that's going on right now in HD research. There are **over 60 companies** working in the HD space right now. There are 13 clinical studies currently recruiting for HD and many more are being planned. We heard very positive clinical trial updates from four companies just this year for potential disease-modifying drugs.

We are living in the age of clinical trials for HD! It would be fantastic if every single one of these companies knocked it out of the park every time. Unfortunately, that wouldn't be realistic. It's of course disappointing when a trial is halted, but the fact that there are dozens of other companies looking to start new trials should be encouraging.

It's not about how many times you get knocked down, it's about how many times you stand back up. So while today may have knocked us down, tomorrow we'll dust ourselves off, and stand back up.

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

GLOSSARY

Food and Drug Administration The government regulatory authority in the US responsible for approving new drugs

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.
