Putting it in print: GENERATION HD1 study results published

Data from GENERATION HD1, the Phase 3 clinical trial testing the huntingtin-lowering drug tominersen, have just been published in a scientific journal. The trial ended a while back, so why is this an important milestone, and what's next?

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The outcomes of the GENERATION HD1 trial have just been published in a scientific journal, nearly three years after the study was halted. In March of 2021, the HD community was hit with the difficult news that the GENERATION HD1 study of Roche's huntingtin-lowering drug, tominersen, faced a halt in dosing. Since then, the data has been analysed, the findings have been shared, and based on what was learned, a new study continues to recruit globally, called GENERATION HD2.

Today marked another milestone in the history of tominersen's development: the results of GENERATION HD1 were published in a widely-read scientific journal. The conclusions remain the same, but peer review and print documentation are immensely important for the progress of science. In this article we'll recap the key messages, explore the impact of published research, and talk about what's next.

What was GENERATION HD1?

The process of "peer review" is key in science.

Image credit: Benis Arapovic

Tominersen is a drug being tested in people to see whether it can help slow or stop symptoms from worsening in adults with HD. It is a type of genetic therapy, known as an antisense oligonucleotide - ASO for short - that is delivered with spinal injections. From an earlier trial we knew that it could lower huntingtin, the protein thought to be harmful to the brain in HD. GENERATION HD1 was a longer, larger Phase 3 study, in which people received a high dose of tominersen every 8 weeks or every 16 weeks.

Unfortunately, the trial had to be halted, in March 2021, when an independent safety monitoring committee found that the safety risks outweighed any potential benefits. In fact, those who got tominersen every 8 weeks seemed to have worse symptoms than those who got no drug at all, by some measurements. Since then, Roche analysed the data and presented it to scientists, doctors, and the community as new information was unearthed.

The most important finding came from an after-the-fact investigation known as a "post hoc" analysis. It seemed that people who began the trial at a younger age, with less severe symptoms, *may* have benefitted from tominersen. For this reason, a new trial of tominersen was designed, called GENERATION HD2. This trial began in 2023, and is testing tominersen in a younger population with earlier HD symptoms.

Today's news: a published study

If you're thinking "all this is old news," well, you're not wrong! The latest breaking research is presented at conferences, like the annual CHDI HD Therapeutics conference that HDBuzz tweets and summarises. This allows scientists to get critical research out to the world as soon as possible. All previous updates about GENERATION HD1 thus far have come from scientific conferences. Published research takes a bit longer; after it's written up, it goes through a process of "peer review" where the data and findings are scrutinised by an outside group of experts.

Peer review keeps science unbiased, fair, and balanced. However, it also causes a bit of a delay, which is why published results from GENERATION HD1 are just coming out now. A new publication in the New England Journal of Medicine details all of the findings from GENERATION HD1. The main message remains the same: GENERATION HD1 did not reach its primary endpoints, tominersen wasn't safe or effective at a high, frequent dose, but there might be some promise at a lower dose, in folks at earlier stages of HD.

What's in the new paper?

The main body of the paper presents these key findings, and a massive appendix gets into the nitty gritty on the methods and the statistics. Some new, formal speculations are made about the connection between measurements of different substances in the blood, and changes observed in symptoms. However, the early halt and the variability of the data make it difficult to draw definite conclusions.

The study authors think that tominersen itself may not have caused direct damage or “shrunk” brain tissue. Instead, they theorise that these side effects could have instead been due to the high dose, which caused some inflammation. People with earlier signs of HD may have had more resilient cells, which is why some may have got some benefit from the huntingtin lowering effects of the drug.

Why is scientific publication a milestone?

Roche chose to make their findings public and accessible to the research community and HD families during the course of the long period of data analysis that led to this paper. And we’re not intending to reopen old wounds by bringing up the disappointment surrounding this trial.

Publication of clinical study results in a medical journal is a big deal. It means that other scientists and doctors, outside of Roche and those who ran the study, were tasked with rigorously looking through the data, evaluating the approach, and recommending ways to improve how it was presented.

This process of “peer review” is key in science: it can lead to new, better experiments, clearer explanations, and more minds thinking about a difficult problem. When a clinical study of Huntington’s disease appears in a well-known journal like this one, the science and the community gets more visibility from scientists and doctors and news outlets.

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What’s next for tominersen

Ultimately, the best way to determine whether tominersen has potential as an HD treatment is to test the theory put forth in this publication. GENERATION HD2 does just that - the study is testing tominersen at a lower dose in people who are most likely to benefit from it. It’s a smaller, “dose-finding” study designed to determine what amount of drug is safest.

There are a few other differences between GENERATION HD1 and HD2.

- Loading dose: In GENERATION HD1, participants were given a dose of tominersen initially before the first dose to boost levels of the drug in their bodies. GENERATION HD2 doesn’t include this “loading dose.”
- Amount of drug: GENERATION HD2 is testing a lower dose of tominersen. While GENERATION HD1 tested 120mg, GENERATION HD2 includes a high dose of 100mg and a low dose of 60mg.

- Frequency: Tominersen is given less frequently in GENERATION HD2. While GENERATION HD1 tested tominersen given every 8 and 16 weeks, participants in GENERATION HD2 receive tominersen every 16 weeks.

The trial, open since early 2023, continues to recruit people with early HD symptoms, ages 25-50, at study sites all over the world.

Steady strides towards HD therapies made possible because of community participation

Importantly, the publication of this manuscript is also a chance to reflect upon and recognise the contributions of the nearly 800 participants, supported by their friends and family, who selflessly enrolled in the GENERATION HD1 trial. Clinical trials are extremely complicated experiments without guaranteed outcomes, and the brave contributions of all the trial participants have substantially moved HD research forward.

Many critical advancements in HD research have only been possible thanks to the steadfast contribution of HD community members. The gene that causes HD was discovered through the participation of HD families from Venezuela - 18,000 people that spanned 10 generations! The genetic modifiers that contribute to differences in age of onset were discovered thanks to the 4,000 people with HD in the Gem-HD Consortium study. Now, advancements in the age of clinical trials are being made thanks to selfless study participants. It's encouraging that the results of the GENERATION HD1 study have been added to the growing scientific literature.

Leora Fox works at the Huntington's Disease Society of America, which has relationships with pharmaceutical companies, including Roche. Sarah Hernandez is an employee of the Hereditary Disease Foundation, for which several of the authors of the scientific publication described in this article serve as members of the Scientific Advisory Board. For more information about our disclosure policy see our FAQ...

GLOSSARY

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

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

therapeutics treatments