Sad News from Roche and Ionis - ASO Trial Halted Early

Disappointing news from Roche and Ionis; the phase III Tominersen huntingtin-lowering trial has been halted early

By Dr Jeff Carroll and Dr Rachel Harding **March 23, 2021**

Edited by Dr Leora Fox

Very sad news was announced today as Roche and Ionis declared that the large ASO study they're running in Huntington's disease patients has been halted early. Importantly, no specific new safety concerns were raised so far, but nevertheless dosing of the study drug, tominersen, as well as the placebo, has been stopped prematurely. What does this mean, and where do we go from here?

Background - what's this trial doing?

Roche and Ionis have developed tominersen which is a type of drug called anantisense oligonucleotide, more commonly referred to as an ASO. ASO therapies are able to reduce the levels of specific protein molecules by interfering with the genetic message which normally tells the cells of our bodies to make that protein. In the case of tominersen, this ASO drug interferes with the huntingtin protein genetic message. Tominersen treatment lowers the levels of both regular and Huntington's disease versions of the huntingtin protein .

This is not the first tominersen clinical trial. Before getting to this phase III study, tominersen was first tested in a Phase I/II trial where it was assessed for safety and shown to lower the levels of huntingtin protein in HD patients. The aim of this current phase III trial, also called the GENERATION-HD1 trial, was to work out if tominersen was effective, not only at lowering huntingtin protein in a larger group of patients, but also if it helped improve signs of HD in patients already showing symptoms.

What happened?

On March 22nd, 2021, a press release from Roche revealed that thephase III study of tominersen had halted dosing on the advice of the Independent Data Monitoring Committee (iDMC). This committee is a group of independent experts who have been monitoring the data from the ongoing study since it began.

These data monitoring committees play a very important role in clinical trials - their job is to act as a neutral party by looking at the data emerging from the trial, without an interest in the trial outcome. So, by design, these committees are totally separate from the patients, physicians and drug companies involved in running the study. Their sole job is to monitor the trial periodically to determine whether or not it should continue.

In general, these committees are asking two kinds of questions - first, are there any unexpected safety concerns emerging? If, for example - all the people receiving a drug had started to have some very weird symptom, this committee would see that and order the trial halted. Secondly, these committees can determine whether ongoing trials look extremely unlikely to have any benefit for the patient participating.

For example, earlier HD studies of several drugs have been halted by this kind of early analysis because the data suggest that the patients are extremely unlikely to benefit from the drug. If folks's HD symptoms are clearly not getting better, then the risk/benefit calculation for giving experimental drugs to people has shifted, and it may no longer be worth it to continue the trial.

What do we know?

What we know is very limited, which is important to remember for the next few weeks and months. All the important facts we know from the press release come from these few sentences:

"The decision was based on the results of a pre-planned review of the data from thePhase III study conducted by an unblinded Independent Data Monitoring Committee (iDMC). The iDMC made its recommendation based on the investigational therapy's potential benefit/risk profile for study participants. No new or emerging safety signals were identified for tominersen in the review of the data from this study."

That tells us a couple things. First, that there's no new "safety signals" - meaning no new bad medical outcomes for the people in the trial. If there had been, say, sudden heart attacks in patients getting the drug (there weren't!!), this press release would have to tell us that. So, thankfully for the families participating, there's not yet any sign of scary new symptoms that emerged.

Second, the press release says that they decided to halt dosing in the trial because of the "investigational therapy's potential benefit/risk profile for study participants." So how could the benefit/risk profile have changed if there's not scary new symptoms that emerged? Bottom line - we don't know yet. However, hypothetically speaking, it could be that the drugs worsen HD symptoms. Or, hypothetically, it could be that the drug just doesn't make HD symptoms better, in a way that is obvious to someone who has access to all of the data, and so it's not worth the risk of exposing people to a new drug because the benefits aren't clear.

Importantly - not even the researchers at Roche and Ionis know the answer to those hypothetical questions right now. When things like this happen, the independent committees have to make their decisions and let everyone know at once. So, until you see another HDBuzz story about this, tune out any noise you hear about these results - there's a huge amount we just don't know.

What do we not know, and when will we know it?

Why have we gotten this cryptic press release for something so important? Unfortunately, the way this works is that when trials are halted like this, there's an initial press release that's released as soon as the companies found out about the news. This is both so that the patient community can be informed, and to prevent shenanigans with people learning the news and selling stocks, or other inappropriate things.

As an example, after today's news Ionis's stock fell by nearly 19%, representing more than a billion dollars worth of value lost. In the wrong hands, early access to this information could be mis-used.

For the patient community, this means that when we hear bad news like this, there's always a baffling gap between this initial warning that something hasn't gone right, and learning the details of exactly what's happened. This is incredibly frustrating, but just how it goes when we hear things like this.

Is HTT lowering a bad idea?

We're likely to see a lot of discussion - and rightly so - about whether loweringhuntingtin protein is a bad idea. Based on all the science we had at the time, we believed it was right to run this trial. And we have this incredible new set-point, which is that we know we can lower huntingtin protein in HD patients. So when we design the next trials - and there will be more trials - we're not going back to square one, but rather a point at which we know that lowering huntingtin in patients is possible.

What's next?

Until we see the data, there's no way to predict what will happen next. But here are some ideas that are sure to be discussed: first, should we be trying to treat HD patients earlier, even before they have advanced symptoms? Second, should we be trying to only lower mutant huntingtin protein (as Wave Life Sciences is currently trying to do in their ongoing study)? Third, should we be trying to lower huntingtin more or less than we did in this trial? You can bet that folks at Ionis and Roche are talking about this right now, as are other HD scientists around the world.

Meanwhile, even though dosing has been permanently stopped in the GENERATION-HD1 trial, Roche intends to continue monitoring participants to measure the longer term safety and effects of tominersen.

Gratitude for patients, physicians and companies

This trial was an enormous undertaking. The HD patients who volunteered in these early trials are forever HD heroes who took on significant risk for themselves on behalf of the entire HD community. Researchers in basic science labs, at both Ionis and at Roche, worked tirelessly to design the best possible drug for testing. And everyone who worked in clinics around the world to test the drug labored relentlessly to see if the drug worked. Everyone involved - families, scientists and physicians - wanted another outcome, but we just didn't get it this time.

Onwards

There's no doubt about it - this is a sad day for the HD community. HDBuzz is feeling sad and disappointed right along with you. But this trial was run in a way that is going to help us better understand how to design the next trial, and what we learn from this setback will be incredibly informative for the worldwide HD research community. And this community - both HD families and HD scientists - have proven that they can do hard stuff together, so we'll shake ourselves off and do it again. And we'll keep doing it until HD is no longer a threat to ourselves and our loved ones.

Dr. Leora Fox works at the Huntington's Disease Society of America, which has relationships and non-disclosure agreements with pharmaceutical companies, including Roche. Dr. Rachel Harding and Dr. Jeff Carroll have no conflicts to declare. 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

huntingtin protein The protein produced by the HD gene.

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

phase III The phase in the development of a new treatment where clinical trials are conducted using many patients, to determine whether the treatment is effective

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.

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is

also called HD and IT-15
