

## Success! ASO drug reduces levels of mutant protein in Huntington's disease patients

Amazing news from Ionis and Roche! HTRx drug successfully lowers harmful huntingtin protein in spinal fluid



By Dr Jeff Carroll

December 11, 2017

Edited by Dr Tamara Maiuri

In an announcement likely to stand as one of the biggest breakthroughs in Huntington's disease since the discovery of the HD gene in 1993, Ionis and Roche today announced that the first human trial of a huntingtin-lowering drug, IONIS-HTRx, demonstrates that it reduces mutant huntingtin in the nervous system, and is safe and well-tolerated.

### What's this huntingtin-lowering stuff all about?

The therapy we're most excited about for Huntington's disease is called **huntingtin-lowering**. You might also hear this approach called **gene silencing**, but huntingtin-lowering is more accurate, as we'll explain.



*Ionis pharmaceuticals has licensed IONIS-HTRx to Roche following this successful Phase 1/2a Study*

Everyone has two copies of the HD gene - one they inherited from their mom, and the other from dad. In people destined to develop HD, one of these copies of the HD gene is changed, or **mutated** in a very specific way.

Right near the beginning of the HD gene is a repetitive sequence that reads, in the code used by scientists to describe DNA, **C-A-G**. People who won't develop Huntington's Disease have around

20 repetitions of this sequence, while in people destined to develop HD, it's longer, most commonly 40 CAG repeats or more.

Our cells use genes as recipes to build proteins – little molecular machines that do useful stuff in cells. When a cell needs to make more of a certain protein, copies of the instructions are made in a chemical closely related to DNA, called RNA. Scientists call this scratch copy of a gene the **messenger RNA** because it carries each gene's information from the DNA to the cells protein building machines.

This means there's more than one place in the cell where we can find the information in the HD mutation - the abnormally long repeat found in peoples' DNA is also copied into the messenger, RNA. Ultimately, cells use this RNA message as instructions for constructing a protein – the **huntingtin protein**.

Most research in HD suggests it's the huntingtin protein, not its gene or messenger, that causes brain cells to malfunction and die in people with HD. But what we know for sure is that every single person with HD has a mutated copy of the HD gene, which acts as the blueprint for the toxic protein. This makes the mutant HD gene enemy number one for those of us working to develop new therapies.

The rapid advancement of science over the last few decades has given scientists a big toolbox for selectively shutting down specific genes. Some techniques, like **antisense oligonucleotides** have been around for decades. Newer techniques, notably genome editing tools like **CRISPR/Cas9** have only been discovered and developed over the last few years.

While the details of the technologies differ, in the HD world, they all have an exciting potential application - to reduce the amount of the huntingtin protein. In numerous animal trials, using a wide range of these silencing tools, when researchers shut down the abnormal huntingtin gene, animal models of HD get better, or never get sick in the first place.

That's cool science, but nobody really cares about curing Huntington's disease in a mouse, or a fruit fly or a worm. We want to cure HD in the species that matters most to us – humans with HD.

## **Reminder: what's the history of this drug and trial?**

Amongst all the huntingtin-lowering technologies that exist, the most developed approach is called **antisense oligonucleotides** or **ASOs**. These are short, custom-built, chemically-modified pieces of DNA that can freely enter cells. Once inside, they locate and help destroy a specific messenger RNA - in this case, the one instructing cells how to make the huntingtin protein.

Ionis Pharmaceuticals, in Carlsbad California, has been developing ASOs for a range of diseases for decades. Years ago, they realized that HD was a perfect fit for their technology, because we know that if, in animals, we reduce the levels of the huntingtin protein in the brain, we improve their HD-like symptoms.

“In the Phase 1/2a study, dose-dependent reductions of mutant huntingtin were observed among patients treated with IONIS-HTTRx ”

Last year Ionis had a massive success with an ASO for another brain disease called **spinal muscular atrophy** (SMA). Those trials tested whether an ASO delivered to the spinal fluid could help improve the condition of babies born with this horrible fatal illness. Same basic technology, but targeting a different gene.

Kids in the Ionis SMA trial did so well that regulators asked them to *halt the trial early*, so that every kid in the study, including those getting the placebo, could receive the drug. Basically, if the disease had taken its normal course, the kids would have gotten progressively weaker and died. But many of the kids treated with the drug were getting stronger and living much longer.

Ionis' SMA drug was subsequently approved in the US, EU and many other countries, and is now being given to children with SMA around the world.

## So, what about HD?

Ionis has been working on **antisense oligonucleotides** (ASOs) for HD since the early 2000s, first in simple cells and then moving into several different animal species. The effects they were seeing were promising, and testing in humans became a real possibility. Anticipation built in 2013 when pharmaceutical giant Roche announced a partnership with Ionis to develop the ASO drug for HD, which they call *\*IONIS-HTT Rx\**. This brought huge resources and experience at Roche to bear on the problem of Huntington's disease.

In July 2015, the most exciting drug trial so far in Huntington's disease began - one in which an ASO designed to reduce production of huntingtin protein was actually delivered to people with HD. The trial was designed to test the safety of the drug and whether or not the drug could do what it was designed to do - reduce the production of the huntingtin protein. We were really excited about this trial starting, and wrote about the trial launch [here](#).

In any drug development effort, the first goal has to be ensuring the drug doesn't have toxic side effects. History provides us with many examples of drugs that seemed like a good idea, but had unexpected side effects when given to people.

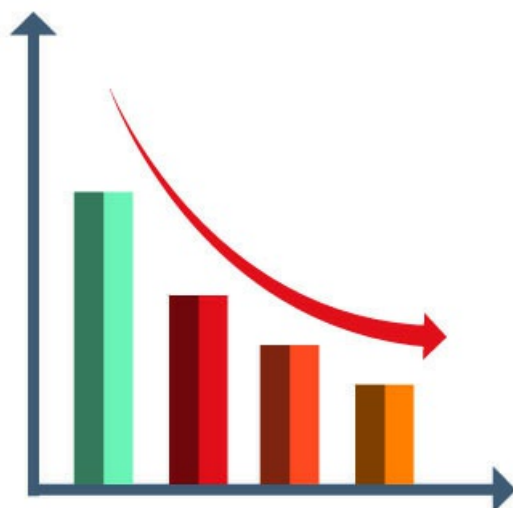
With this in mind, Ionis and Roche designed a study whose main aim was determining whether the drug is safe when administered to people, which has to be the first step in the drug development process.

This first study enrolled 46 people with early HD symptoms in Germany, Canada and the UK. The trial began in July 2015 and was planned to end in November, 2017. As you'll see, the whole trial happened right on schedule, which doesn't always happen!

Before we talk about results, there are a few important details for people to keep in mind. First, ASO drugs do not get into the brain if swallowed in a pill form. As a consequence, ASO drugs for brain diseases are delivered by injecting them at the base of the spine, using a technique called

**lumbar puncture**. It sounds a little scary, but it's actually a very common procedure, done thousands of times per day in hospitals around the world.

Second, this study included a **placebo** arm. That means that some of the participants went through all the steps, but received injections without drugs. This is an absolutely critical component of trials - if we don't have a group of people without drug, how can we be sure that changes we observe are due to the drug, and not some other factor?



*Dose-dependent reductions of mutant huntingtin protein were seen in the spinal fluid from patients who received the drug*

Finally, dose. Any time researchers give a drug to people for the first time, they start with a very low dose. In a trial like this, formally called a **multiple ascending dose** study, the first participants receive a low dose and then participants who join later receive higher doses of the drug. This enables doctors to carefully monitor people on each new dose, so any negative effects of treatment are caught early.

## What has happened now?

On Monday, December 11th, Ionis put out a press release describing the main results of the first study of IONIS-HTTRx. The headline was: "Ionis pharmaceuticals licenses IONIS-HTTRx to partner following SUCCESSFUL Phase 1/2a Study in patients with Huntington's Disease". It also said: "Dose-dependent Reductions of Mutant Huntington Protein Observed".

If you're wondering how excited you should be about this - both HDBuzz editors indulged in a little bit of happy dancing when they saw the press release. It's **really** big news!

We'll explain why this is so exciting soon, but there's a few things to keep in mind.

First - safety. Ionis and Roche very carefully monitored the subjects in the trial to look for any signs that the drug is not safe. In the press release, Ionis reports: "the safety and tolerability profile of

IONIS-HTTRx observed in the Phase 1/2a study **supports continued development**". That means there were no significant safety issues observed in the participants, so the first hurdle for this drug in HD has been cleared and we can move on to the next steps.

Remember – this trial was not designed to prove that IONIS-HTTRx helps with HD symptoms or progression. The primary goal of this study was to establish that the drug is **safe**. The first time you put a new drug into someone's body, you want to expose as few people as possible, in case there are unexpected safety problems.

Also, remember that this study was short - each patient only received 4 months of injections. This is too short a time to look for changes in the rate of HD progression. Even if IONIS-HTTRx turns out to be a wonder drug, the impact on symptoms after only 4 months of treatment could be tiny, and we would not expect to detect them in such a small trial.

So – and this is a really important message – **we won't know yet whether the drug made peoples' HD symptoms better.**

However, the trial was able to go beyond safety in one important way. Every time the volunteers in the trial were given a dose of the drug, a sample of their cerebrospinal fluid - which bathes the brain and spinal cord - was collected.

Previous work had demonstrated that the levels of the huntingtin protein can be measured in the cerebrospinal fluid. It seems that, as cells are becoming sick during the course of HD, some of their contents are spilled into this fluid, which circulates around the brain.

“The key now is to move quickly to a larger trial to test whether IONIS-HTTRx slows disease progression ”

Since the goal of huntingtin lowering therapies like IONIS-HTTRx is to reduce the amount of the huntingtin protein in vulnerable brain cells, in theory this gives us a great way to tell whether the drug is doing what it's meant to do. We simply measure levels of huntingtin protein in the cerebrospinal fluid before and after drug treatment.

We think the most exciting news in today's press release from Ionis is this: “In the Phase 1/2a study, **dose-dependent reductions of mutant huntingtin** were observed among patients treated with IONIS-HTTRx”. Frank Bennett, Ionis' chief scientist, went as far as to state that the reductions seen “substantially exceeded our expectations”.

This means that patients treated with IONIS-HTTRx have reductions in the huntingtin protein in their cerebrospinal fluid. Based on this result, it looks like the drug is doing what it's meant to do, and that huntingtin lowering has been achieved!

The **dose-dependent** bit means that higher doses of the drug lead to lower levels of huntingtin in their spinal fluid. That's really nice evidence that the effect observed is really due to the drug, and not some other aspect of the treatment.

# Now what?

This is big, and everyone in the HD community should be thankful to the brave volunteers who signed up for a demanding trial, as well as their families and caregivers. We should also be thankful to Roche, and particularly Ionis, who believed in this approach and worked for many years to get to this point.

But we're not done yet! What's next?

First, we have to conduct a trial with sufficient numbers of people, and a long enough treatment, to impact the course of HD symptoms. The success of this first trial sets the stage for a larger study in hundreds of HD patients, as soon as possible.

The researchers involved in this study know how urgent the need for the next trial is. In the press release, the primary investigator of the study, Professor Sarah Tabrizi, said: "the key now is to move quickly to a larger trial to test whether IONIS-HTTRx slows disease progression". Roche's firm opt-in, announced today, is a great sign that such a trial can be expected soon. As soon as details are released, you'll read about them on HDBuzz.

This is a great day in the HD community, and it sets us on the path to even more exciting work in 2018. For the first time in history, HD patients are being treated with drugs **known** to reduce the amount of huntingtin protein in their brain. Until we conduct the next trial, we won't know if this reduces the impact of HD. And while we know the drug is safe in the short term, we will also have to watch carefully for any long-term adverse effects. But we're facing this problem with renewed excitement and hope. It's the best early Christmas present we could have hoped for.

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*HDBuzz co-founder Ed Wild is an investigator on the Ionis HTTRx program and member of the Scientific Advisory Boards for Ionis and Roche. That's why this piece was written by Jeff Carroll. Jeff collaborates with Ionis on mouse studies, but was not involved in this trial. Tamara Maiuri has no conflict of interest to declare. [For more information about our disclosure policy see our FAQ...](#)*

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## GLOSSARY

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

**CSF** A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

**huntingtin protein** The protein produced by the HD gene.

**gene silencing** An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

**Genome Editing** The use of zinc-finger nucleases to make changes in DNA. 'Genome' is a word for all the DNA we each have.

**messenger RNA** A message molecule, based on DNA, used by cells as the final set of instructions for making a protein.

**CRISPR** A system for editing DNA in precise ways

**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

**RNA** the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.

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