Going boldly: First person treated in Phase 1 clinical trial by Alnylam Pharmaceuticals

A new Phase 1 clinical trial for the huntingtin-lowering drug ALN-HTT02 was initiated this week with the first dose given. Read on to learn details about the trial and how it compares to other ongoing huntingtin-lowering trials in the clinic.

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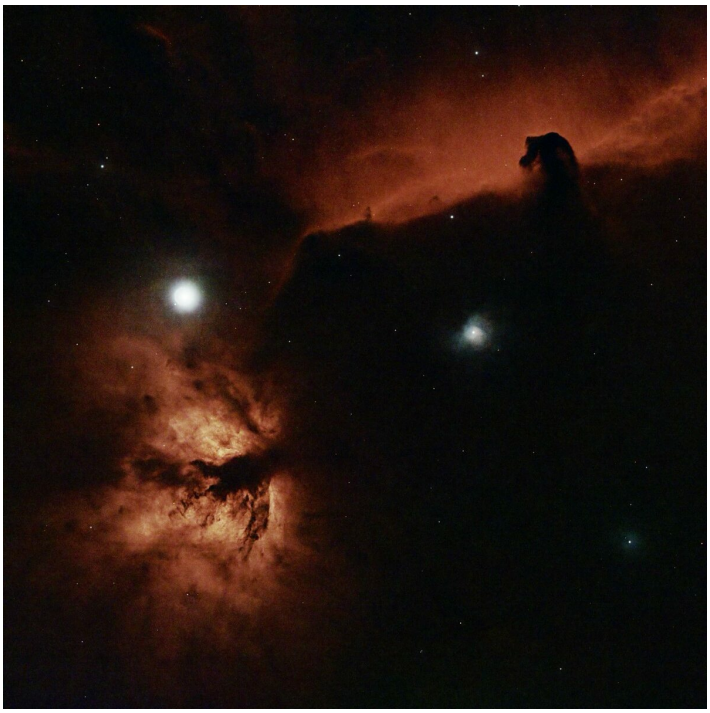
On December 3, 2024 a study site gave word that the very first person received a new drug, called ALN-HTT02, as part of a Phase 1 trial aiming to treat Huntington's disease (HD). Going boldly as the first human ever to receive this drug, they're charting a course that we all hope will one day lead to a disease-modifying drug for HD. Let's dig into the details of this new trial!

Who is behind this new trial?

In September, Alnylam Pharmaceuticals announced that they were launching a clinical trial to test their huntingtin-lowering drug. A spelling error in the gene huntingtin, called HTT for short, is what causes HD. Those who inherit this spelling mistake in HTT will go on to develop changes with mood, movement, and memory as HD progresses. Lowering levels of the HTT molecule with the spelling mistake is one strategy being tested in the clinic to potentially treat HD.



Alnylam is named for the celestial bridge that connects the Earth and stars, hoping to be the link with successful clinical trials for a future without Huntington's disease.

Image credit: HDBuzz's own Dr. Ed Wild!

Alnylam is a relative newcomer to the scene of HDtherapeutics, but they're not new to drug discovery. They've been around for 22 years and received commercial approval for their first drug 6 years ago. They also have experience with other brain disorders; they're currently advancing towards a Phase 2 trial for a drug that they hope will treat Alzheimer's disease.

The company is named for the bright center star in the constellation Orion's belt, "Alnilam". As that star has been used for thousands of years by navigators, it symbolizes Alnylam's passion for discovery. For some, this star represents a bridge between earthly and celestial realms. Hopefully all these positive cosmic analogies are good luck and Alnylam's drugs can bridge us to an HD-free future!

Molecular Mars Rovers

The drug that Alnylam is developing in collaboration with Regeneron Pharmaceuticals that is being tested in this trial is called ALN-HTT02. It works through a mechanism called "RNA interference", also known as RNAi. RNAi is unique because it takes advantage of molecular machinery that already exists inside cells for processing - like little Mars Rovers processing samples from the red planet. RNAi is Alnyam's specialty. They developed the world's first RNAi-based medicine! (A drug used to treat a nerve disease.)

ALN-HTT02 itself is a piece of synthetic genetic material that contains a code to recognize HTT. Once it's introduced into a cell, the cell's own molecular machines are used to process the synthetic genetic material. This creates a fragment of the synthetic genetic material that binds to the HTT message to lower it.

ALN-HTT02 targets the first bit of the HTT gene called “exon 1”. This is the part of the genetic message that contains the spelling error that causes HD. Researchers think that exon 1 could be the key to driving toxicity that builds up over time, damaging brain cells. Hopefully by specifically targeting this area, that damage will be lessened, or stopped altogether.

> **“Phase 1 trials are the first time that drugs developed in the lab are ever given to humans! Knowing that they’re safe and well tolerated by people is the first step in advancing them in the clinic. ”**

Same twinkle, different star

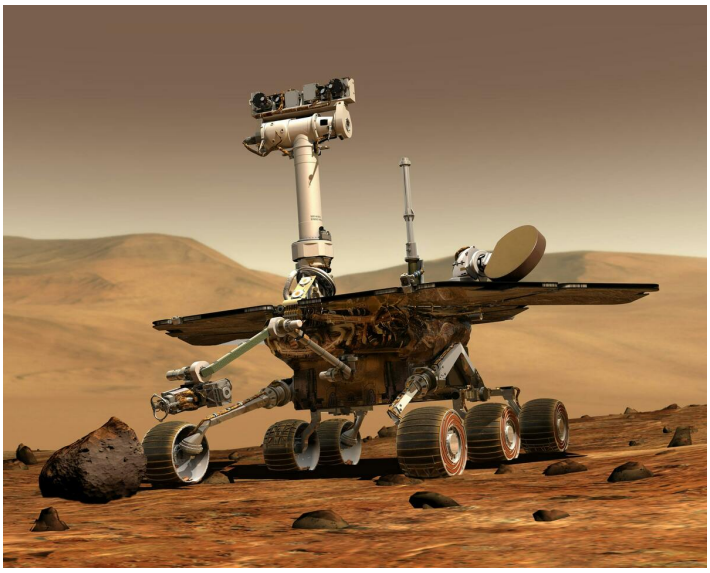
Other ongoing clinical trials are taking a similar approach - targeting HTT to lower levels. While there are similarities to these other trials, there are also some subtle differences.

Like most other trials, ALN-HTT02 is what we call “total HTT” lowering. That means it targets both copies of the HTT gene, the one from mom and the other from dad. This means that both regular HTT and the HTT with the spelling mistake are lowered. Other companies, like Wave Life Sciences and Vico Therapeutics, are running trials that specifically or preferentially target only the copy of HTT with the disease-causing spelling mistake.

There are currently quite a few HTT lowering drugs being tested in clinical trials, but the way the drugs actually lower HTT levels differs. Companies like Wave, Vico, and Roche are using something called an antisense oligonucleotide, or an ASO. This is a short piece of genetic material that binds the HTT message molecule to lower levels. So it doesn’t use the cell’s molecular machinery to produce the message-binding fragment the way that RNAi does.

Companies like PTC Therapeutics and Skyhawk Therapeutics are using something called splice modulators that target HTT to lower levels. These are small molecules taken as a pill that target the way the HTT message molecule is processed, causing it to be sent to the cell’s trash can, like the waste containment units on the International Space Station. (Clearly there are only so many relevant space analogies…)

Similar to Alnylam, uniQure is using an RNAi-based approach. The difference between uniQure and Alnylam though is that uniQure’s drug AMT-130 is carried in a harmless virus and delivered via brain surgery. Conversely, Alnylam’s ALN-HTT02 isn’t encapsulated in a virus and is delivered via spinal injection.



RNA interference, or RNAi, works by using the cell's own molecular machines to process synthetic genetic material, like the Mars Rover processing samples on an alien planet.

Overall though, all of the drugs being tested by these companies have the same goal - lower the HTT message to hopefully reduce the toxic effects of the protein with the goal of slowing or stopping HD.

Details about the trial

ALN-HTT02 is being tested in Phase 1 trial. As with all Phase 1 trials, theprimary goal of this study will be to determine if it is safe. Phase 1 trials are the first time that drugs developed in the lab are ever given to humans! Knowing that they're safe and well tolerated by people is the first step in advancing them in the clinic.

They'll also look at how well the drug targets HTT and how levels change in the CSF, the fluid that bathes the brain. They'll use clinical tests to measure symptoms, but would need a larger trial with different measures to understand if ALN-HTT02 works to change clinical features of HD.

Up to 54 people with Stage 2 or early Stage 3 HD between the ages of 25 and 70 are being recruited for this trial. **Recruitment age is notable here**, as most trials exclude those over the age of 65.

Currently, recruitment is only open at two sites in the UK, but the study is also being initiated in Canada and recruitment in additional countries is expected to follow.

> **"We are profoundly grateful to these brave volunteers who help answer questions about new drugs, taking the first steps across the bridge to a future without HD. "**

Participants will be given a single dose of ALN-HTT02 via spinal injection during the trial. A portion of the participants will be given a placebo, an injection that contains no active drug. After 6 months, those who received the placebo will be given the option to receive an

injection that contains ALN-HTT02.

Guided by the stars

As our first trial participant steps boldly into a future unknown, guided by a company that is inspired by the stars, we hope this charts a new path for HD therapeutics. Phase 1 trial participants are incredibly brave, like astronauts walking courageously into the unknown.

We are profoundly grateful to these brave volunteers who help answer questions about new drugs, taking the first steps across the celestial bridge to a future without HD.

The authors have no conflicts of interest 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

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

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

therapeutics treatments

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.

Exons The small fraction of our DNA that is directly used to instruct cells how to make proteins

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

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15