Steady progress from uniQure - promising data to end the year

uniQure ushered in the end of the year by releasing some promising data from their huntingtin-lowering gene therapy trials

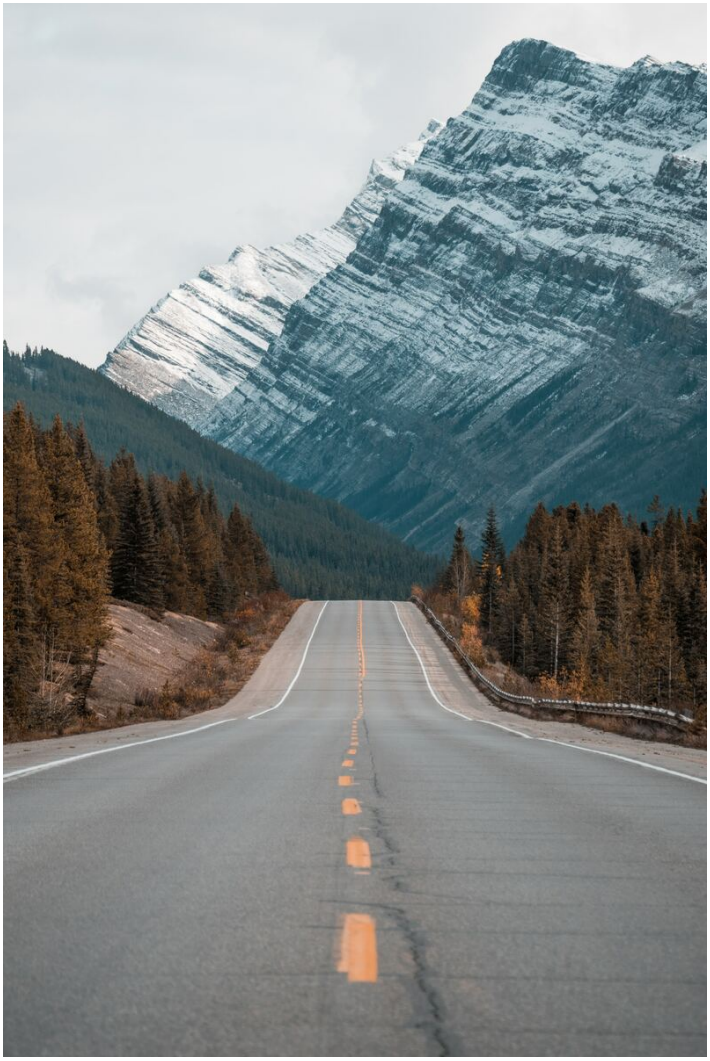
By Dr Leora Fox | December 20, 2023 | Edited by Dr Rachel Harding

---

With the holidays approaching, welcome news arrived on December 19th in a press release from uniQure. The latest data from the HD-GeneTRX studies of AMT-130, an experimental huntingtin-lowering gene therapy, shows that the drug still appears to be safe over the course of a few years. Since the number of participants is very small, we cannot yet draw conclusions about the effectiveness of AMT-130 to treat HD, but there are early, promising signs that AMT-130 holds potential to stabilize some symptoms. This means that the trial can safely continue and will hopefully expand in future.

A refresher on the HD-GeneTRX trials

First, let's talk about the history of the first gene therapy for HD. Developed by uniQure, AMT-130 involves a harmless virus packaged with genetic material that is designed to lower the amount of huntingtin protein in the brain. We've covered a bit more on the science of this in a 2019 article. It was first thoroughly tested in many different animal models of HD before the current human safety studies, known as HD-GeneTRX-1 and HD-GeneTRX-2, began in 2020.



uniQure's gene therapy clinical trials are steadily progressing and showing promising data

AMT-130 is delivered via a single surgery into the fluid-filled spaces of the brain, known as ventricles, with the goal of permanently lowering levels of huntingtin in brain cells. Across the two studies in Europe and the USA, there have been 39 participants who underwent surgery. We've talked more about the different groups involved in the study in a previous article. Overall, most have received AMT-130, with some receiving a low dose, some a high dose, and a few undergoing a "sham" surgery as a control. After 1 year some of those in the "sham" surgery group also received a high dose of the drug.

As the trial has unfolded, uniQure has periodically shared data along the way. HDBuzz covered these releases, discussing positive 12-month data in 2022, a [safety hiccup]https://en.hdbuzz.net/329 that led to a pause in high-dose surgeries, and then the resumption of the trial late last year. In mid-2023, the trial was continuing to proceed smoothly with some positive data emerging. Today, some of the participants have been followed up to 30 months, and the data continues to look promising.

The latest data release

uniQure issued a press release and held an investor call to share the latest data from the trial. Let's break down the news into digestible chunks related to AMT-130's safety, potential impact on participants' symptoms, and biomarkers.

Safety

This is a small study that is designed mainly to test safety and how well people tolerate AMT-130. There are definite risks following a major brain surgery, which we saw with the study pause last year. But with longer monitoring after the surgery and the prescription of anti-inflammatories, these risks are now better controlled.

Additionally, bloodwork, vital signs, heart rhythms and other measures of health were largely normal. Overall, this means that for up to 30 months after the surgery, AMT-130 seems to be safe and well tolerated at the low dose, and there are good options for managing potentially dangerous side effects.

Impact on symptoms

Although this study wasn't designed to determine if AMT-130 can actually slow or stop symptoms, there are many clinical measurements built into the study that can begin to give us a picture of whether this drug can change the course of HD. Because the control group for the HD-GeneTRX studies is so tiny, uniQure also used data that was collected separately through a big observational study that did not involve a drug, called TRACK-HD. They were able to compare data from those who got AMT-130, with data from people at a very similar disease stage who didn't receive the drug. These observational study participants were also followed over the course of at least 30 months.

The studies involved tests that measured movement, day-to-day function, ability to switch thinking tasks, and more. The main positive takeaway here is that those who received the high dose of AMT-130 seem to retain their functional and movement abilities for 18 months, as they performed better on all the tests than the TRACK-HD participants who didn't have the surgery. The data for the low dose extends to 30 months, and these participants showed preservation of movement and function on some measurements.

All that said, much of this data describes a trend and the statistics don't yet allow uniQure to draw a definite conclusion about how well AMT-130 works to slow or halt the signs of HD. There are too few people so far to tell - just 5 or 6 in the low dose group have reached the 30 months mark after their surgery.

> **"Despite the caveats, this is the first time an HD drug has shown the potential to stabilize symptoms "**

Biomarkers

Another important thing that uniQure shared was measurements made in the spinal fluid of participants. Neurofilament light (NfL) is a protein released from brain cells when they are damaged. This is one measurement that scientists use in HD drug studies to get a clearer picture of whether the treatment could be helpful or harmful. After a brain surgery, NfL

levels naturally go way up, but the hope is that they return to normal or “baseline” after a while (sometimes this takes quite a long time). If NfL levels dip even lower, that is one sign that the drug is safe and could even be helping to preserve brain health.

The latest NfL data from this study show that after the surgery, there is a big spike in this biomarker, but in the group that got a high dose of AMT-130, the levels seem to have returned to baseline after 18 months. In the low dose group, NfL levels are below baseline at 30 months - a good safety sign and one piece of the puzzle to show a possible benefit for the brain. Once again, we’re looking at trends in data from a very small group of people.

Since AMT-130 is designed to lower huntingtin, uniQure also wants to understand whether the treated participants have lower levels of huntingtin - but this has proven to be very tricky, not only in this study, but across the HD research field. They weren’t able to get reliable measurements from the spinal fluid for many of the study participants. Scientists at uniQure also suggested that it’s not yet clear whether looking at levels of huntingtin in spinal fluid is the most accurate way to measure the effects of a drug delivered directly to the brain. Still, any positive clinical signs will always outweigh measurements of a biomarker .

What can we take away from the latest data?

Above all, it’s important to remember that this study was designed to test safety and not efficacy, and so far it seems that AMT-130 is safe and tolerable for up to 30 months. It’s also a very tiny data set, and the comparison group was taken from a separate, observational study.

Despite all these caveats, there is reason for some excitement around the latest data shared by uniQure. This is the first time ANY HD study has shown genuine positive signs that a drug has the potential to stabilize symptoms, with safety and side effects that appear to be manageable.

Overall, this is what uniQure hoped to see at this point in the study. There is reason for it to move forward, and to hope that a larger study will be designed to test efficacy. So - no miracles, but a solid body of data that continues to grow. We expect another data release in around six months, in mid-2024.

HD is a slowly progressing disease, and for an unprecedented gene therapy like AMT-130, it’s about the long game. Ensuring that a novel approach is safe and effective can be frustratingly slow, but we are encouraged by the latest data and we will continue to report on any new results that are shared.

In the meantime, we are doing a cautiously optimistic happy dance, and we wish all HDBuzz readers a happy and healthy holiday season.

Rachel Harding has no conflicts to declare. Leora Fox works at the Huntington's Disease

Society of America which has relationships with pharmaceutical companies, including uniQure. For more information about our disclosure policy see our FAQ...

GLOSSARY

huntingtin protein The protein produced by the HD gene.

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

ventricle Normal fluid-filled spaces within the brain.

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

efficacy A measure of whether a treatment works or not
