Moving into the Fast Lane: uniQure and the FDA Are on the Same Track for Accelerated Approval

In an update shared today, uniQure announced alignment with the US drug regulator on key criteria for accelerated approval of drugs for Huntington's disease.


By Dr Rachel Harding and Dr Sarah Hernandez **December 10, 2024**

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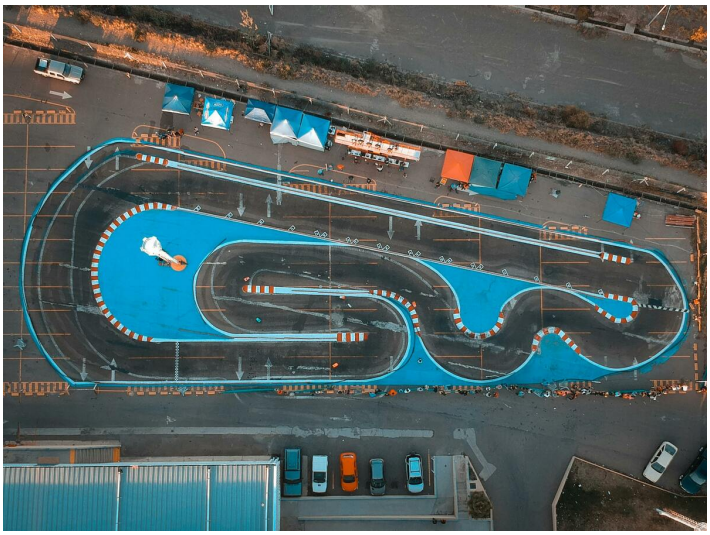
On December 10, 2024 we received a regulatory update from uniQure about their drug, AMT-130, that they're advancing through the clinic for Huntington's disease (HD). On the call, uniQure announced alignment with the FDA on key elements to get accelerated regulatory approval. Of this program, Matt Kapusta, the CEO of uniQure, said that they are going to "advance AMT-130 as aggressively as possible". Today's exciting update is not just good news for uniQure, but also for all other trials for HD, as it maps the road we need to take to get regulatory-approved treatments, and effective drugs for people with HD.

What is AMT-130?

AMT-130 is the first gene therapy that was developed for HD from Dutch pharmaceutical company uniQure. Similar to other therapies for HD currently in clinical trials, it is designed to lower levels of the HD protein, called huntingtin, in the brain.



uniQure and the FDA showed that they're on the same track. Adopting the cUHDRS and NfL metrics for Huntington's disease is an advancement not only for uniQure, but for all clinical

trials for HD.

Image credit: Juan Cruz Palacio Mir

Because AMT-130 is a “one-and-done” gene therapy, this means folks receiving this drug only need one dose in their lifetime. AMT-130 is given by brain surgery, which delivers a non-harmful virus into brain cells, with specific genetic instructions to reduce the production of the huntingtin protein.

Two Clinical Trials in Progress

Two clinical trials are currently in progress to evaluate AMT-130: HD-GeneTRX-1 in the United States and HD-GeneTRX-2 in Europe. Together, these trials have recruited 45 participants, who were randomly assigned to receive a high dose, a low dose, or a sham surgery, where no drug was administered.

Participants in the trials are monitored over years after receiving the drug through a variety of assessments, including clinical evaluations, biomarker analyses, and brain imaging. The primary objective of these trials is to determine the safety of AMT-130. Researchers are also gathering data to explore potential effects of the drug on HD symptoms and other measures.

AMT-130 has had a bit of a bumpy road but data shared by uniQure earlier this year in July seemed to indicate that the drug was generally safe and could even be improving signs and symptoms of HD in some people.

Driving Optimism Forward

Accelerating forward with the positive news from the summer, uniQure met with the FDA to map what would be necessary to get accelerated approval for AMT-130. The FDA did a thorough review of their current data to discuss what steps need to be taken, which hastens the approval process by about 5 years. uniQure feels they now have the pathway to swiftly advance AMT-130 for submission.

There were 3 major takeaways from today’s update from uniQure:

> **“Of this program, Matt Kapusta, the CEO of uniQure, said that they are going to “advance AMT-130 as aggressively as possible”. ”**

- 1) They can apply for accelerated approval based on their current HD-GeneTRX trial data.
- 2) The clinical metric cUHDRS can be used as an intermediate endpoint.
- 3) Spinal fluid levels of NfL, a biomarker of brain cell health, can be used as evidence to support therapeutic benefit.

On Track

uniQure shared that their current HD-GeneTRX studies for AMT-130 are on track for serving as the basis for accelerated approval. Because these are really long studies that follow people for years after receiving the drug, uniQure opted to compare people who received AMT-130 to a natural history study. Natural history studies follow people with HD as they live their day-to-day lives without participating in clinical trials. This lets researchers know how HD naturally progresses without an intervention.

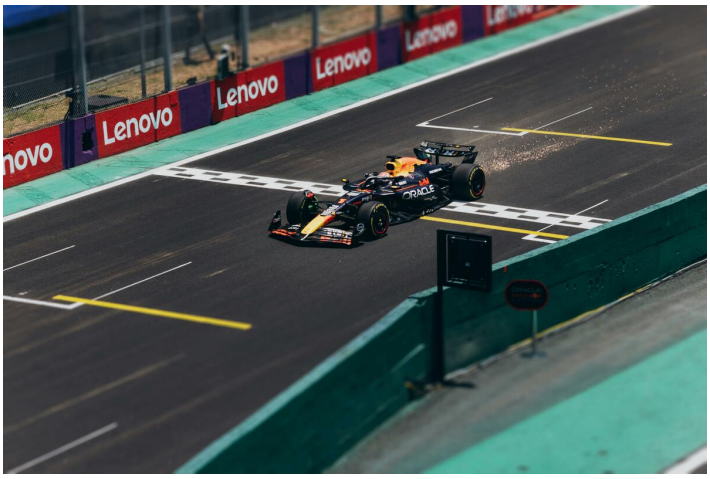
The FDA agreed that uniQure could use a natural history study as a control group before applying for regulatory approval. This means that an additional clinical trial will not be needed and the ongoing HD-GeneTRX studies *may* be the last trial before uniQure seeks FDA approval for AMT-130.

Performance Indicators

uniQure also talked to the FDA about different metrics that they're using, one that follows clinical progression of HD and another that measures health of brain cells.

Clinical Progression

For clinical progression, uniQure is using a collection of tests called the cUHDRS, or the Composite Unified Huntington's Disease Rating Scale. The cUHDRS is a sensitive way to measure clinical progression of HD. Along with the ability to determine how well someone functions day-to-day, the cUHDRS also includes tests that assess movement control, capacity to pay attention, and memory.



For the first time, the FDA detailed what can get treatments for Huntington's disease across the finish line - positive changes in cUHDRS and improvements in NfL levels.

Image credit: Jonathan Borba

Before the cUHDRS, companies were using a test called Total Functional Capacity, or TFC. TFC uses a set of metrics to broadly measure how well someone functions by determining if they can hold a job, do daily chores, and other general tasks of daily life.

While TFC can be helpful for assessing quality of life, it is a less sensitive metric so it can be tricky to use to really determine if a drug is modifying the course of HD. For example, someone may start taking an antidepressant that allows them to keep their job and do better with tasks associated with daily life which would be reflected in a better TFC score, but it hasn't actually altered HD in any way.

In today's call, uniQure shared that the FDA agreed that cUHDRS is a clinically meaningful intermediate endpoint. This is big because it shows that the FDA and HD drug developers are now on the same track - while the FDA had previously told companies that cUHDRS couldn't be used, they've now been convinced otherwise. These discussions come from the same FDA center, the Center for Biologics Evaluation and Research (CBER), with which the HD family community recently met.

Brain Cell Health

uniQure also shared that the FDA agreed that levels ofneurofilament light (NfL) can be used as a metric for therapeutic benefit. NfL is a molecule that's released from brain cells as they're damaged. We know that NfL levels increase as HD progresses. So lots of researchers think that if we can show that a medication can hold NfL levels steady or make them decrease, that suggests improved brain cell health.

NfL is a relatively new marker for brain cell health, but is rapidly being adopted in labs and the clinic. However, it hasn't yet been widely accepted by regulatory agencies. Hopefully today's news represents a change!

Fast track insights

A major takeaway here is that the FDA, **for the first time**, has detailed what it would take to get accelerated approval for a treatment for HD - positive changes in cUHDRS and improvements in NfL levels.

> **"This means that an additional clinical trial will not be needed and the ongoing HD-GeneTRX studies *may* be the last trial before uniQure seeks FDA approval for AMT-130. "**

This is the first pivotal trial that the FDA has given the green light for cUHDRS andNfL. This is big because it opens up the door for other clinical trials to use the same metrics to receive accelerated approval. This matters for all drug developers working to make medicines for HD, not just uniQure, as they now have a clear path laid out for what is expected to get a drug from trials to approval.

Moving toward the finish line

uniQure is keeping the conversation going with the FDA and the HD community. As their trials proceed forward, they are gathering more and more data about how this drug is working. Indeed, soon they'll have 45 patients treated with AMT-130 with the first

participant reaching the 5 year mark in 2025. Because of that, uniQure feels they have a sufficient amount of safety data around AMT-130.

uniQure is planning to meet with the FDA again in early 2025. They're also planning to engage with the European Medicines Agency near the beginning of next year to align with them on a path to approval, similar to how they're working with the FDA.

They said they'll also release more data in 2025 focussed on folks who are 3 years out from surgery, but didn't give specifics about if they feel this data will be necessary before filing with regulatory agencies.

In all, uniQure is racing forward with the goal of receiving accelerated approval for AMT-130. Their progress with the FDA paves a way forward to other companies too. 2025 will certainly be a big year!

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

Total Functional Capacity A standardized rating scale for function in HD, used to assess capacity to work, handle finances, perform domestic chores and self-care tasks

NfL biomarker of brain health

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

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.

endpoint A specific outcome or measurement that researchers use to assess the effectiveness or safety of a treatment. Endpoints are predefined before the trial begins and can be either primary (the main result the trial is designed to evaluate, such as improvement in symptoms) or secondary (additional outcomes of interest, such as quality of life or biomarker changes).