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Greetings to everyone in the Huntington's disease community,

My name is Dan Leonard, and I am the Senior Director of Patient Advocacy here at uniQure. On behalf of the uniQure Huntington's disease (HD) team, I'm honored to introduce our company and our gene therapy clinical development program to all of you. uniQure has a long history in developing gene therapies, but is a relative newcomer to the HD community, so I'd like to provide a bit of background to begin. Before I do that, I'd like to say thank you to the team at the Huntington's Disease Society of America for helping us get this message out to the community.

uniQure was founded as Amsterdam Molecular Therapeutics (AMT) in the Netherlands in 1998. In 2012, the innovative work of our research team there resulted in the first gene therapy ever approved in Europe. This experience laid the foundation for our leadership today in the discovery, clinical development, and manufacturing of gene therapies for rare diseases.

uniQure operates out of two locations, with scientific research and technology centered in Amsterdam, and manufacturing in Lexington, MA. Other functions such as Clinical and Regulatory Affairs, and corporate management span both sites. In addition to HD, uniQure has programs in hemophilia B, hemophilia A, spinocerebellar ataxia type 3 (SCA3) and other rare, life-altering diseases. Our vision is to build an industry-leading gene therapy company and we are honored to work closely with patient communities to bring this vision to a reality.

I referred to uniQure as a gene therapy company, but what is gene therapy? Genes within our cells provide a blueprint to produce proteins. Proteins are essential structural and functional components of all living organisms. DNA variations in genes can cause the blueprint to be wrong – this is the cause of many diseases. Gene therapy provides a way to correct a missing or defective protein, or to reduce the production of an abnormal disease-causing protein. The goal? A single treatment that is administered only once with long-term benefits.

The clinical trial uniQure is planning to conduct in HD uses a gene therapy known as AMT-130. This investigational treatment will be the first one-time administered gene therapy to enter clinical testing for the treatment of HD. AMT-130 is administered only once by neurosurgical procedure. There are two key components to AMT-130, a vector and a gene encoding a microRNA. The vector acts as a delivery system and is based on a non-disease causing adeno-associated virus (AAV) that has been changed to carry and deliver a gene encoding a microRNA that will recognize, bind and non-selectively lower the human huntingtin protein. microRNA (or miRNA) are small pieces of genetic material that can prevent production of a given protein. To "non-selectively lower" human huntingtin protein means that production of both the disease-causing mutant (mHTT) and normal huntingtin protein (HTT) will be decreased.

The objectives of the Phase I/II clinical trial are to assess the safety, tolerability and efficacy of AMT-130 in patients with HD using a dose-escalating, randomized, and double-blinded control design. uniQure expects to open several clinical sites in the United States and begin enrolling patients in the second half of 2019.



For an introduction to how gene therapy works, we created a video that you can watch by [clicking here](#).

We'd also like to take this opportunity to provide more detail about the trial itself, including the reason we're conducting the trial, who might be eligible, what is involved in the study, some of the potential risks and benefits, and other information you might find helpful.

Why is this study being done?

This is the first study testing AMT-130 in humans. The main purpose of this study is to find a safe dose of AMT-130 in adults who have tested positive for the HD gene and who have early stage HD. The study will also look at how the body processes AMT-130 and will explore how AMT-130 might affect how the disease progresses. The therapeutic goal is to inhibit the production of the mHTT by using AAV to deliver genes encoding microRNAs directly to the brain for non-selective lowering of the huntingtin protein.

Who is eligible for the study?

The inclusion criteria include, but are not limited to:

- Patients with a definitive clinical diagnosis of early manifest HD
- Genotype of 44 CAG repeats or greater in the *huntingtin* gene
- Between the ages of 25 to 65 years old

Please note that participants will need to be off any other experimental agents for 60 days prior to enrollment. Previous exposure to gene therapy, huntingtin lowering strategies, or experimental brain surgery are prohibited.

The most important step in determining eligibility would be to speak to a physician at one of the clinical sites. One should always talk to their own doctor as well when making any major medical decisions.

What is involved in the study?

It is important to reiterate that AMT-130 is administered only once. The study will test two dose levels of AMT-130 (low dose and high dose). The safety of the low dose will be assessed before testing the high dose. A total of 26 patients will be enrolled. Of the 26 patients enrolled, 16 will receive treatment with AMT-130 ("Treated Group") and 10 will not receive any study treatment ("Imitation Group"). Patients assigned to the Treated Group will receive the dose of AMT-130 during a neurosurgical visit. AMT-130 will be infused into two specific brain regions (caudate and striatum) under general anesthesia. This is done by drilling two to six small holes in the skull and administering AMT-130 by a micro-catheter. For patients assigned to the Imitation Group, small, superficial holes will be drilled into the surface of the skull under general anesthesia, but they will **NOT** receive a dose of AMT-130. The main part of the study lasts for 18 months, with additional annual visits out to 5 years for continued safety follow up. Procedures will include clinic visits, assessments of physical and neurological health, a neurosurgical procedure, lumbar punctures (LP), brain scans, and samples from body fluids. The study is "double blinded" meaning neither the patient, the investigator or clinical staff will know if the patient is in the Treated Group or the Imitation Group.

What are the possible risks and discomforts?



This is the first study in humans testing AMT-130 gene therapy. Currently, there is no information on the long-term side effects of AMT-130 in humans. AMT-130 has been studied in animals. The doses in this study are based on doses given to animals and were found to be generally safe. Some AAV vectors have been approved for clinical use and are being used in several gene therapy clinical trials. In general, AAV vectors are considered safe. Risks that should be considered are the following:

- Treatment with gene therapy is permanent and cannot be removed once administered.
- AMT-130 lowers both normal and mutant huntingtin protein in animals. The effects of lowering normal and mutant huntingtin protein levels in adults are currently unknown.
- Patients may be ineligible to receive another gene therapy treatment after receiving AMT-130.
- Because AMT-130 is investigational, there may be risks or side effects that are not known at this time. There may be rare and unknown side effects, including reactions that may be life threatening.
- AMT-130 is delivered directly to the brain and will include risks associated with general anesthesia and micro-catheter placement in the brain.

Are there any benefits to taking part in this study?

The goal of this clinical trial is to determine if AMT-130 can lower huntingtin protein levels and slow the progression of Huntington Disease. There may be no therapeutic benefit from participation in this study; however, one may receive benefit from having their HD progression monitored during the course of this study. While the individual may not receive any direct benefit, participation in this research study may help others if AMT-130 is found to be safe and effective.

Is there an open label extension study for patients randomized into the Imitation Group?

It is uniQure's intent to give patients who are randomized into the Imitation Group and successfully complete the trial out to 18 months, the choice to enroll in an open-label extension study in which they are guaranteed to receive AMT-130. This can only be done if the FDA and the study monitoring board review the safety and efficacy data collected in the first 18 months of the trial and deem it acceptable to proceed.

Where is the study being conducted?

Study sites will be located in the United States. The specific location of sites will be updated on an ongoing basis when the site is ready to screen patients for eligibility. To check the status please go to clinicaltrials.gov and/or HDtrialfinder.org where the trial will be listed in the coming weeks.

What are the next steps for the trial?

The uniQure HD team is working as quickly as possible to get sites ready for screening patients for eligibility. We hope to enroll the first patients in the second half of 2019. We will continue to work with the team at HDSA to communicate important information to the community when appropriate. In the meantime thank you for your interest in our program. The entire uniQure HD team look forward to working with the community to make progress in developing a treatment for Huntington's disease.