Title: A Randomized, Double-blind, Placebo-controlled Study, to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intrathecally Administered Single Ascending Doses of ALN-HTT02 in Adult Patients with Huntington's Disease

Brief Title: A Study to Evaluate ALN-HTT02 in Adult Patients with Huntington's Disease

EU Trial Number: 2024-515732-68-00

WHY IS THIS RESEARCH NEEDED?

Huntington's disease (HD) is an inherited disease that causes nerve cells in the brain to slowly stop working and die. Researchers think HD is caused by a change (called a **mutation**) in the Huntingtin gene (**HTT**) that is passed down from a parent (inherited). This means the child of a parent with HD has a 50% chance of inheriting the gene that can cause HD.

Symptoms of HD usually start when a person becomes an adult. HD can affect a person's movements, thinking ability, and behavior. HD gets worse over time. Medicines are currently available to help manage HD symptoms of movement, thinking and behavior but cannot prevent them. A person with HD will often lose their mobility, ability to speak, and need help with all daily activities.

Researchers are studying **ALN-HTT02,** which works differently than currently available medicines. People with HD have mutant HTT protein (or **mHTT**). ALN-HTT02 targets how certain genes communicate, called **mRNA**, which can help stop the production of proteins associated with disease. Researchers are testing whether ALN-HTT02 can potentially decrease the level of mHTT and slow down or stop the disease from progressing.

WHAT ARE THE GOALS OF THIS STUDY AND HOW WILL THEY BE MEASURED?

Researchers are testing **ALN-HTT02** to see if it causes any medical problems and if it can keep HD from getting worse over time.

Goals for the Study	How Researchers Measure the Goals
Primary	
To find out if ALN-HTT02 causes medical problems for participants with HD.	• Record all medical problems, called **adverse events** that happen to participants while they are in the study.
Secondary	
To see how ALN-HTT02 changes certain proteins in the fluid around the spine of participants with HD.	• Record the change in levels of **mHTT** protein in participants while they are in the study.
To find out how ALN-HTT02 moves through and out of the body after 1 dose is given.	• Measure the amount of ALN-HTT02 in samples of blood plasma, urine, and fluids taken from the spine.

WHO CAN TAKE PART IN THE STUDY?

This study includes up to 102 adults with HD. Participants are between the ages of **25 to 70 years old.** The study has about 20 locations across Europe and North America.

HOW IS THE STUDY DESIGNED?

A participant may be in the study for up to about 2 years. The study has 2 parts:

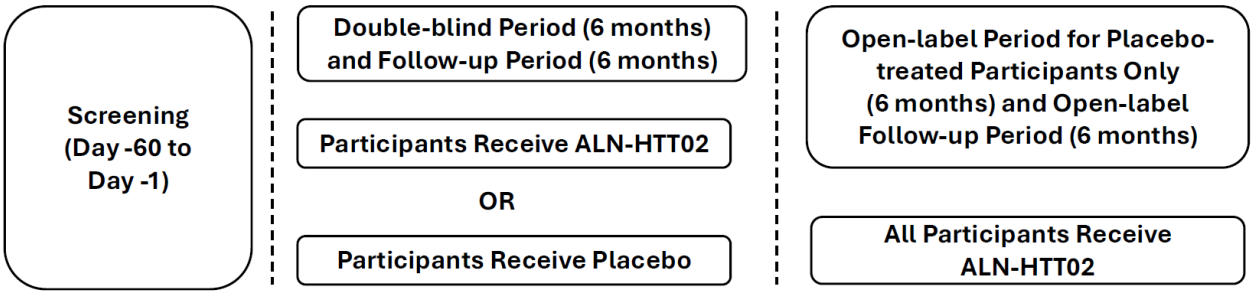
- **Double-blind Period**: The first 6 months of the study is called the Double-blind Period. Participants will receive a **single dose** of ALN-HTT02 or a placebo. A placebo looks like ALN-HTT02 but doesn't

contain any medicine. In this part of the study neither the participants nor the study doctor will know who is given ALN-HTT02 or placebo. This is called a **double-blind**. After the Double-blind Period ends, the participants and the study doctor will find out whether ALN-HTT02 or placebo was given. Participants who received ALN-HTT02 during the Double-blind Period will not receive another dose of ALN-HTT02 but will continue being in the study for a Follow-up Period of 6 months.

- **Open-label Period**: Participants who received placebo during the Double-blind Period can choose to receive a **single dose** of ALN-HTT02 after the Double-blind Period ends. Participants will have the same tests over 6 months as they did during the Double-blind Period. Both the doctors and the participants know that ALN-HTT02 will be given to all participants. This is called **open-label**. After the Open-label Period ends, the participants will continue in the study for another 6 months as part of a Follow-up Period.

Study doctors will check overall health and ask participants how they feel after getting the dose. Study doctors will also take blood and samples of the clear fluid that surrounds and cushions the spinal cord (called cerebrospinal fluid or **CSF**) to check safety and see how the study medicine works.

Other tests to check for possible medical problems and overall safety that happen during the study include laboratory tests, electrocardiograms (ECGs), physical exams, and checking vital signs like blood pressure, temperature, and pulse rate.



HOW WILL THE STUDY MEDICATION BE GIVEN?

ALN-HTT02 and placebo will be given as an injection into the fluid around the spine, or CSF.

WHAT RISKS AND BENEFITS WILL PARTICIPANTS EXPERIENCE?

Researchers think that ALN-HTT02 may have an impact on how the symptoms of HD progress. Researchers do not think that ALN-HTT02 will cause serious or severe medical problems. This is based on studies in animals. People may or may not benefit from the treatment received during the study. More information on the benefits and risks is available in the protocol.

WHERE CAN I LEARN MORE ABOUT THE STUDY?

For more details on this study please speak with a doctor, or visit:
https://euclinicaltrials.eu/ Use the study identifier **2024-515732-68-00**