

Title:	TRITON-PN: A Phase 3, Global, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Nucleosiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy (hATTR-PN)
Short Title:	TRITON-PN: A Phase 3 Study to Evaluate the Efficacy and Safety of Nucleosiran in Patients with Hereditary Transthyretin Amyloidosis with Polyneuropathy
EU Trial Number:	2025-522544-40

WHY IS THIS RESEARCH NEEDED?

Researchers want to learn more about the safety and effects of nucleosiran in participants with hereditary transthyretin-mediated amyloidosis with polyneuropathy (**hATTR-PN**). hATTR-PN is a rare and serious disease caused when a protein called transthyretin (**TTR**) forms abnormal deposits called **amyloid**. TTR amyloid deposits in the nerves lead to **neuropathy**, or nerve damage. Symptoms of neuropathy include numbness, tingling, weakness, diarrhea and constipation. TTR amyloid can also affect the heart. Without treatment, people with hATTR-PN may lose their ability to walk and eventually die from the disease.

Today, there are a few medicines approved to treat hATTR-PN, but they do not work well for all people. Researchers are testing a new type of medicine called **nucleosiran** in this study and in other ongoing studies. Nucleosiran is designed to lower TTR protein levels and therefore reduce the build-up of TTR amyloid deposits. By lowering the amount of TTR protein in the body, researchers hope that nucleosiran might slow down or stop hATTR-PN from getting worse.

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

Researchers are testing to see if nucleosiran is safe and effective for the treatment of hATTR-PN. For some of the goals below, researchers will compare participants who receive nucleosiran in this study to participants who received a placebo in a prior study. This is called an **external placebo** because it was given outside the current study. A placebo looks like a study medicine but doesn't contain any medicine. None of the participants in this study will receive a placebo.

Researchers will also compare participants who will receive nucleosiran to participants who will receive vutrisiran, a medicine already approved for hATTR-PN.

Primary Goal for the Study	How Researchers Measure the Primary Goal
To evaluate the effects of nucleosiran on nerve problems.	Determine the change in neuropathy symptoms using a test called the Modified Neuropathy Impairment Score at Month 9, comparing nucleosiran to the external placebo.
Secondary Goals for the Study	How Researchers Measure the Secondary Goals
To understand the effect of nucleosiran on quality of life.	Determine the change in quality of life scores based on participant responses at Month 9, comparing nucleosiran to the external placebo.
To understand how TTR protein in the blood responds to nucleosiran at different times during the study.	Record the change in TTR protein levels found in samples of blood collected at Week 6, Month 9, and Month 18 of the study, comparing nucleosiran to vutrisiran.
To evaluate the effects of nucleosiran on nutrition.	Determine the change in body mass index (BMI) at Month 9, comparing nucleosiran to the external placebo.
To assess how nucleosiran affects nerve problems, quality of life, nutrition, disability, and walking speed over a longer time period.	Determine the change observed in several tests to measure neuropathy symptoms, quality of life, BMI, disability and walking ability at Month 18, comparing nucleosiran to the external placebo.

WHO CAN TAKE PART IN THE STUDY?

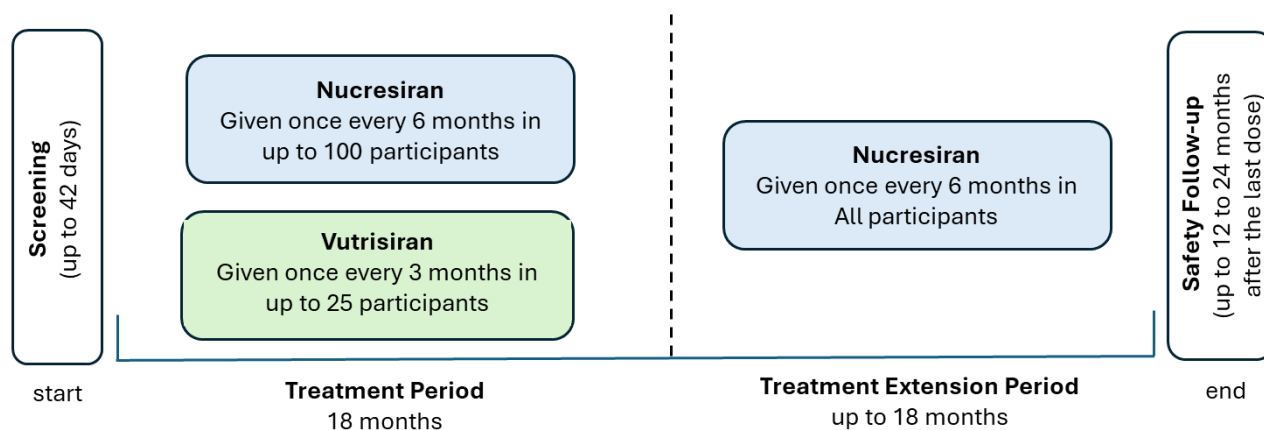
About 125 men and women who are between 18 and 85 years old with a diagnosis of hATTR-PN will be enrolled in the study. Participants will have a genetic test that shows a change (or variant) in the TTR gene and other tests to confirm they have neuropathy. People who are taking other medicines for hATTR-PN called TTR stabilizers can participate after stopping the medicine for a period of time. However, people who are taking other medicines for hATTR-PN to lower their TTR levels cannot join the study.

HOW IS THE STUDY DESIGNED?

The study has 4 parts starting with a **Screening Period** when researchers will check to make sure participants are eligible to join the study.

- **Treatment Period** (18 months): Participants will be assigned by chance to receive nuresiran once every 6 months or vutrisiran once every 3 months. Both the study doctors and the participants will know that all participants will receive nuresiran or vutrisiran. This is called an **open-label**.
- **Treatment Extension Period** (up to 18 months): All participants are able to join the treatment extension period within 9 months of their last dose of study medicine in the treatment period. All participants will receive open-label nuresiran once every 6 months.

Throughout the study, doctors will monitor participants for any medical problems (called adverse events). Study doctors will also conduct physical exams, perform tests on the nerves and blood, and assess quality of life to determine if nuresiran is effective. After the last dose in the treatment extension period, participants will start the **Safety Follow-up Period**. No study medicine will be given during this period. Each participant may be in the study for up to **62 months**.



HOW WILL THE STUDY MEDICINE BE GIVEN?

The study doctor will give nuresiran or vutrisiran as an injection under the skin.

WHAT RISKS AND BENEFITS WILL PARTICIPANTS EXPERIENCE?

Researchers think nuresiran may help reduce symptoms of neuropathy in people with hATTR-PN, but it is not certain if all participants will benefit. Possible side effects include injection site reactions, liver problems, and low Vitamin A levels. More information on the benefits and risks is available in the study protocol.

WHERE CAN I LEARN MORE ABOUT THE STUDY?

For more details on this study please speak with a doctor, or visit:

www.clinicaltrials.gov or www.clinicaltrialsregister.eu.