Title:	InsigHHT: A Phase 1/2, Randomized, Double-blind, Placebo-controlled, 2-part Study of the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of Single Dose ALN-6400 in Adult Healthy Volunteers and Multiple Dose ALN-6400 in Adult Patients with Hereditary Hemorrhagic Telangiectasia (HHT)
Short Title:	InsigHHT: A Phase 1/2 Study to Evaluate ALN-6400 in Healthy Volunteers and in Patients with HHT
EU Trial Number:	2025-522510-23-00

WHY IS THIS RESEARCH NEEDED?

Researchers want to learn about the safety and effects of the study medicine (**ALN-6400**) for a bleeding disorder called **Hereditary Hemorrhagic Telangiectasia (HHT)**. HHT causes fragile, abnormal blood vessels to form in the body. HHT also leads to abnormal connections between arteries and veins called **arteriovenous malformations (AVMs)**.

People with HHT often have sudden and severe nosebleeds when these abnormal blood vessels burst and start bleeding. Other symptoms include bleeding from the digestive tract, low levels of healthy red blood cells (called anemia), and medical problems like heart failure or stroke due to AVMs in the liver, lungs, or brain.

Currently, there are no widely approved medicines for the treatment of HHT. Tranexamic acid (**TXA**) is approved in many countries for other bleeding problems and can help reduce the bleeding symptoms of HHT. TXA has side effects and requires the patient to take many pills. In this study, researchers are testing ALN-6400 to see if it can reduce the production of a protein in the liver called **plasminogen**. Plasminogen plays a key role in helping the body break down blood clots. By lowering plasminogen levels in the blood, researchers expect to stabilize the blood clots and reduce bleeding symptoms in people with HHT.

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

This study includes 2 parts, Part A and Part B. The main goal for Part A is to understand the dose of ALN-6400 that is safe and effective in healthy participants. Information on Part A is available in the protocol. The main goals for Part B will further test the dose from Part A in people with HHT as described below.

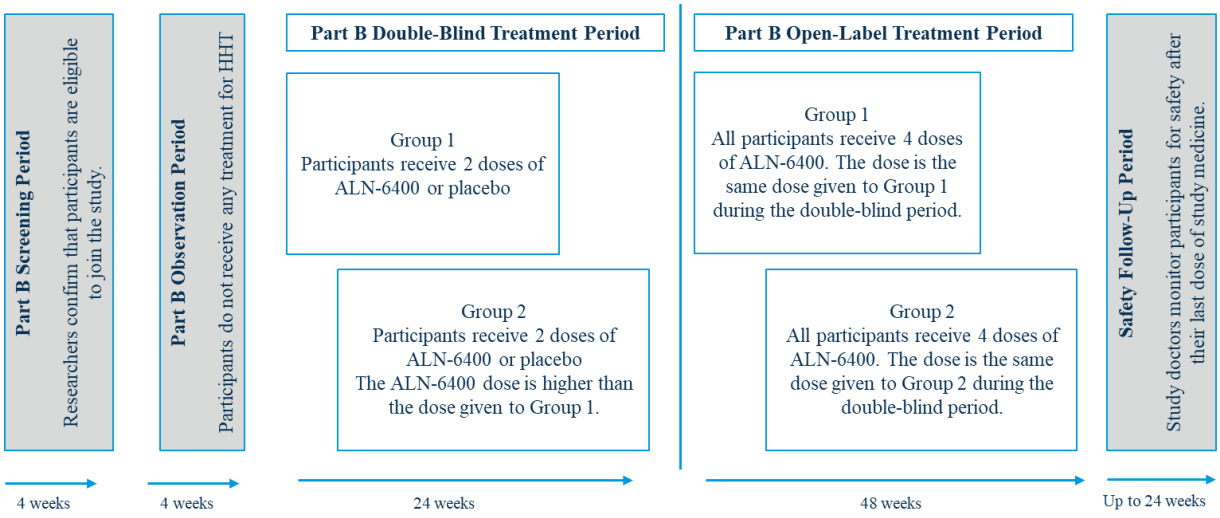
Primary Goals for Part B of the Study	How Researchers Measure the Part B Goals
To check if multiple doses of ALN-6400 are safe for people with HHT.	Record the number of medical problems (called **adverse events**) that participants experience.
Secondary Goals for Part B of the Study	**How Researchers Measure the Part B Goals**
To see if ALN-6400 lowers plasminogen levels in the blood compared to placebo.	Measure the change in plasminogen level in the blood.
To see how multiple doses of ALN-6400 effect: • Nosebleeds • Blood or iron problems • Quality of life	Observe and record the change from baseline in: • Intensity, duration, frequency, and the number of days without a nosebleed • Scores taken from lab tests • Participants' answers to questions about quality of life

WHO CAN TAKE PART IN THE STUDY?

Part A of the study includes up to 72 healthy adult volunteers between 18 and 65 years old. Part B includes about 48 adult participants with HHT. People with abnormal laboratory tests who are taking certain medicines cannot participate in the study. All of the criteria to join the study are defined in the protocol.

HOW IS THE STUDY DESIGNED?

- **Part A (up to 41 weeks):** Healthy participants are assigned by chance to receive a single dose of ALN-6400 or placebo. A placebo looks like study medicine but does not contain any medicine. Neither the participant nor the study doctor knows who is given a placebo or ALN-6400. This is called a **double-blind period**.
- **Part B (about 104 weeks)**: Includes 2 treatment periods:
    1. **Double-Blind Treatment Period**: 2 groups of participants with HHT are assigned by chance to receive 2 doses of ALN-6400 or placebo. Each group receives the first dose at the start of the period, and the second dose later during the period.
    2. **Open-Label Treatment Period**: The same 2 groups of participants with HHT receive 4 separate doses of ALN-6400 as described below. **Open-label** means that both the doctors and the participants know that all participants receive ALN-6400. No placebo is given.



HOW WILL THE STUDY MEDICINE BE GIVEN?

Study medicine will be given as an injection under the skin.

WHAT RISKS AND BENEFITS WILL PARTICIPANTS EXPERIENCE?

This is the first study of ALN-6400 in people. Earlier studies in animals have shown that ALN-6400 should be generally safe and well-tolerated. However, some possible risks of taking ALN-6400 may include developing growths that feel firm or "woody" (called ligneous lesions) and blood clots. Researchers closely monitor participants for any signs of ligneous lesions, blood clots, and any abnormal lab tests.

It is unknown if ALN-6400 will help improve HHT, and participants in the study may receive no direct benefit. Information from this study may help others with the same condition in the future. More details about these risks can be found in the study protocol.

The information in this document is up to date and reflects the version of the clinical trial protocol in use.