Givosiran

An Investigational RNAi Therapeutic for Acute Hepatic Porphyrias

Overview

- Givosiran (ALN-AS1) is an investigational, subcutaneously administered RNA interference (RNAi) therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) in development for the treatment of acute hepatic porphyrias (AHPs).
- AHPs are a family of rare, genetic diseases characterized by potentially life-threatening attacks and, for many patients, chronic debilitating symptoms that negatively impact daily functioning and quality of life.
- Currently, there are no treatments approved to prevent debilitating attacks and treat the chronic symptoms of the disease.

Clinical Development

- Givosiran is being studied in a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study called ENVISION as a once-monthly subcutaneous (under the skin) injection in approximately 75 patients. The study is evaluating whether givosiran, by lowering ALAS1, can reduce buildup of the neurotoxic intermediates, aminolevulinic acid (ALA) and porphobilinogen (PBG), and prevent attacks and chronic symptoms.
- The primary endpoint is the annualized rate of porphyria attacks over six months.
- Key secondary and exploratory endpoints in ENVISION will evaluate reductions in chronic symptoms of AHPs, such as pain, nausea, and fatigue, that impact daily functioning and quality of life.
- A planned interim analysis, agreed upon with the Food and Drug Administration (FDA), will evaluate reduction in biomarker levels - aminolevulinic acid (ALA) - that may reasonably predict clinical benefit. Reduction in ALA will be evaluated in 30 patients after three months of dosing.

Regulatory Designations

- Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA)
- Priority Medicines (PRIME) designation by the European Medicines Agency (EMA)
- Orphan Drug designations in both the U.S. and the European Union

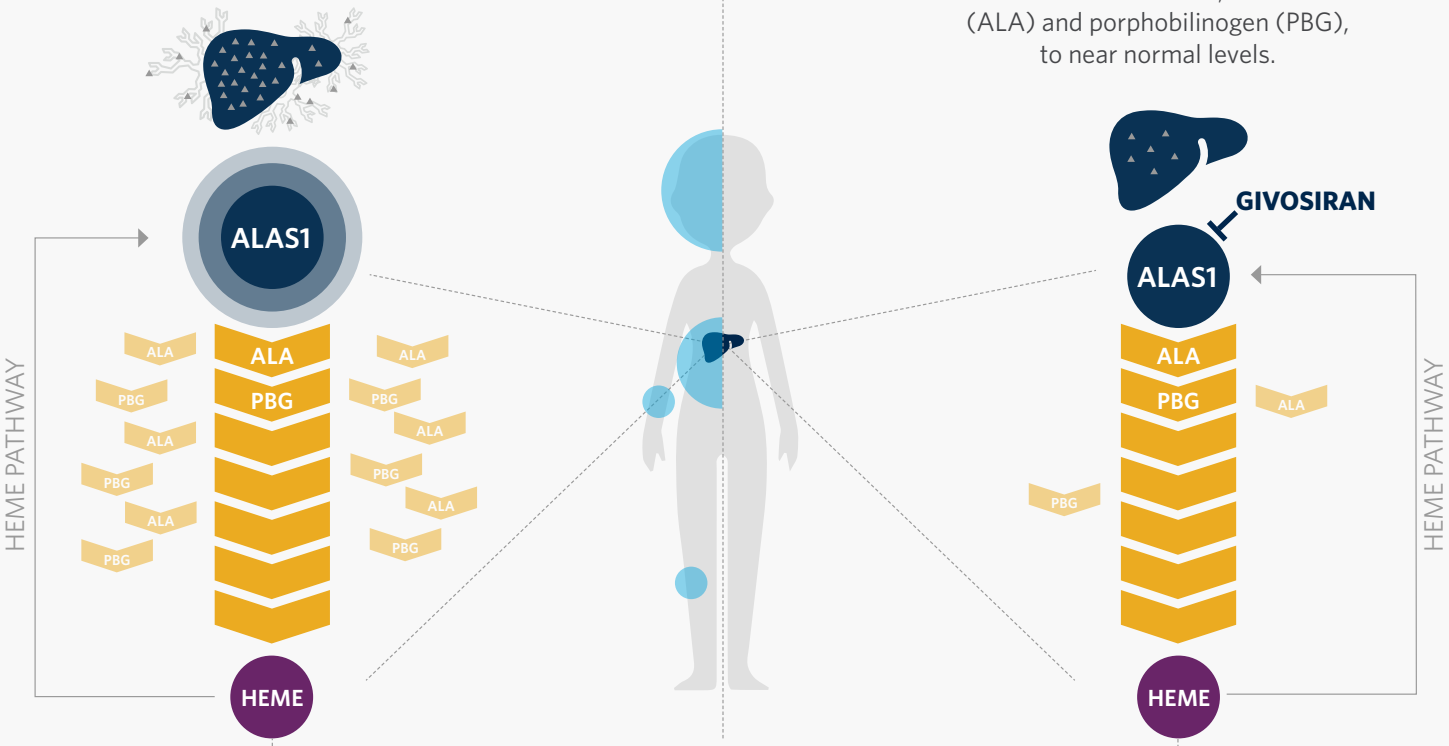
Mechanism of Action

AHPs Pathway

In people with AHPs, 1 of the 8 enzymes in the pathway that creates heme is deficient.

Pathway Stabilization with Givosiran

Monthly administration of givosiran has the potential to significantly lower induced liver ALAS1 levels in a sustained manner and thereby decrease neurotoxic heme intermediates, aminolevulinic acid (ALA) and porphobilinogen (PBG), to near normal levels.



Heme originates from the liver and plays a role in removing toxins and other enzyme-related processes.

Certain triggers can result in increased levels of ALAS1, which leads to the accumulation of heme neurotoxic intermediates – aminolevulinic acid (ALA) and porphobilinogen (PBG) – and can cause the attacks and chronic symptoms characteristic of AHPs.

- Certain Drugs
- Food Restriction
- Alcohol
- Stress
- Smoking
- Hormonal changes

For more information about givosiran, please contact media@alnylam.com.