Givosiran

An Investigational RNAi Therapeutic for Acute Hepatic Porphyria

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 porphyria (AHP).
- AHP refers to a family of rare, genetic diseases characterized by potentially life-threatening attacks and, for some 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, global, multicenter, Phase 3 study called ENVISION as a once-monthly subcutaneous (under the skin) injection in patients with a documented diagnosis of AHP. 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 requiring hospitalization, urgent healthcare visit, or hemin administration at home over the six-month treatment period.
- Key secondary and exploratory endpoints will evaluate reductions in the hallmark symptoms of AHP, such as pain, nausea, and fatigue, as well as impact on quality of life.

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

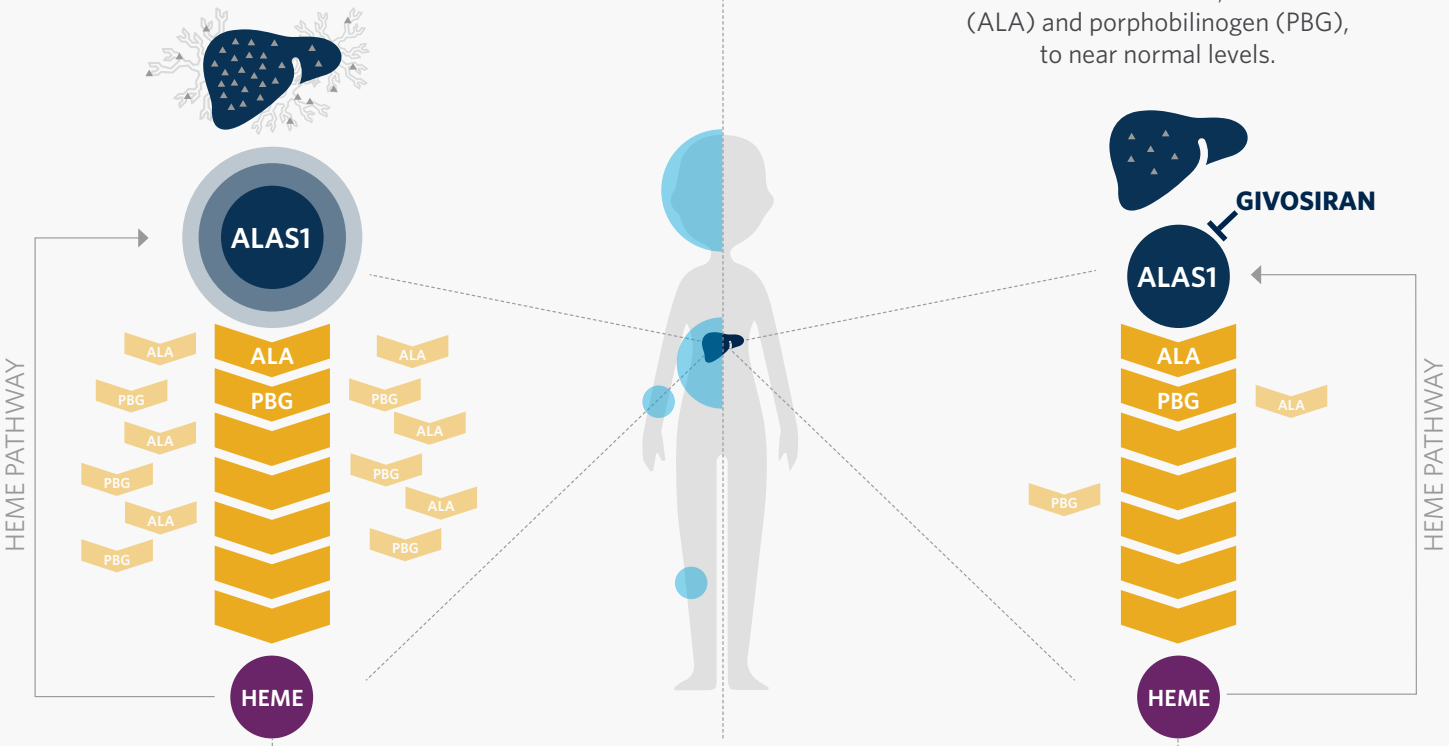
Mechanism of Action

AHP Pathway

In people with AHP, one of the enzymes in the pathway that creates heme in the liver 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 AHP.

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

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