Givosiran

National Cancer Institute

Source

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A proprietary enhanced stabilization chemistry (ESC)-stabilized conjugate composed of the liver-targeted ligand N-acetylgalactosamine (GalNAc) conjugated to small-interfering RNAs (siRNAs) directed against the liver-expressed enzyme aminolevulinic acid synthase 1 (delta-aminolevulinate synthase 1; ALAS1; ALAS-1) that can potentially be used in the treatment of acute hepatic porphyrias (AHPs). Upon subcutaneous administration of givosiran, the GalNAc moiety targets and binds with high affinity to asialoglycoprotein receptors (ASGPRs) expressed on hepatocytes. Once inside the cell, the siRNAs bind to and silence ALAS1 mRNA and inhibit both the translation and expression of the ALAS1 protein. This prevents delta-aminolevulinic acid (ALA) formation, decreases 5-ALA levels and prevents the production of porphyrins and hemes, such as porphobilinogen (PBG). AHPs are a group of metabolic disorders caused by deficiencies of specific enzymes that are responsible for hemoglobulin biosynthesis within the liver, which leads to the accumulation of toxic intermediates, such as ALA and PBG. ALAS1, a liver-expressed, rate-limiting enzyme in the heme biosynthesis pathway, is responsible for the formation of ALA from succinyl-CoA and glycine. ESC enables the subcutaneous dosing of givosiran with increased efficacy, durability and a wide therapeutic index as compared to non-ESC GalNAc-siRNA conjugates.