ENVISION Clinical Trial Overview

*Givosiran is an RNA interference (RNAi) therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) approved in the U.S. as GIVLAARI® (givosiran) for the treatment of adults with acute hepatic porphyria (AHP).**

About Acute Hepatic Porphyria (AHP)

Acute hepatic porphyria (AHP) refers to a family of rare, genetic diseases characterized by potentially life-threatening attacks and, for some patients, chronic debilitating manifestations, including pain, that can negatively impact daily functioning and quality of life. AHP is comprised of four types: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and aminolevulinic acid (ALA) dehydratase-deficiency porphyria (ADP).

In people with AHP, enzyme defects in the liver's heme biosynthesis pathway result in an increase of ALAS1, which in turn, leads to an accumulation of ALA and porphobilinogen (PBG) in the body—the neurotoxic heme synthesis intermediates associated with AHP attacks and other disease manifestations.

ENVISION

The ENVISION Phase 3 study was a randomized, double-blind (DB), placebo-controlled, global, multicenter trial designed to evaluate the efficacy and safety of givosiran in patients with AHP.

The trial enrolled 94 patients (including 89 patients with AIP, the most common type of AHP) across 36 sites in 18 countries, and is the largest interventional study ever conducted in AHP.

During the 6-month DB period, study participants were randomized 1:1 to receive a monthly subcutaneous injection of givosiran at 2.5mg/kg or placebo.

Upon completion of dosing in the DB period, all eligible patients (93 out of 94; 99 percent) enrolled in the open-label extension (OLE) period of up to 30 months.

6-Month DB Endpoints

- The primary outcome measure was the annualized rate of composite porphyria attacks (AAR), defined as those attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home, in patients with AIP.
- Secondary endpoints included urinary levels of ALA and PBG, days of intravenous hemin use and daily worst pain in patients with AIP, and AAR in all patients with AHP. Additional secondary endpoints were daily worst scores for fatigue and nausea, as well as the change from baseline in the score on the Physical Component Summary of the 12-Item Short-Form Health Survey 2 (SF-12) in patients with AIP.
- Key exploratory endpoints included the use of analgesics (opioids and non-opioids), findings on the Patient Global Impression of Change (PGIC)—a measure of health status—and results of the Porphyria Patient Experience Questionnaire (PPEQ), which measured the change in the perceived treatment experience and ability to function and perform daily living activities in patients with AIP and AHP.

6-Month DB Results

- Relative to placebo, treatment with givosiran resulted in a statistically significant and clinically meaningful mean reduction of 74 percent in the AAR.
- Improvements were observed in a number of secondary endpoints, including reductions in urinary ALA and PBG levels and days of intravenous hemin use. Improvements were also observed in worst daily pain, as measured by a post-hoc Wilcoxon signed-rank test.
  - There were no statistically significant between-group differences in the scores for daily worst fatigue or nausea.
- Patients receiving givosiran experienced favorable effects in exploratory endpoints related to use of analgesics (opioids), overall health status, and daily functioning compared to those receiving placebo.
  - The percentage of patients with AIP using any opioids during the DB period was lower in the givosiran group (67 percent) when compared to placebo (88 percent).

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  - In the PGIC, 59 percent of patients with AHP receiving givosiran reported their overall status since the beginning of the study was "very much improved" or "much improved" compared to 18 percent of the placebo-treated patients reporting "much improved."
  - In the PPEQ, patients with AHP receiving givosiran reported improvements in activities of daily living compared to patients receiving placebo, including traveling for work or pleasure (35.1 percent vs. 13.2 percent, respectively) and participating in social activities (35.1 percent vs. 7.9 percent, respectively). Patients receiving givosiran also reported improvement in daily functioning compared to placebo, including doing household chores (35.1 percent vs. 5.3 percent, respectively), and exercising moderately (32.4 percent vs. 5.3 percent, respectively), as well as satisfaction with treatment (72.2 percent vs. 13.5 percent, respectively).
- In patients with AHP, the most common adverse events observed in the givosiran group (reported in ≥25 percent of patients) were nausea (27 percent) and injection site reactions (25 percent). Other adverse events seen more frequently (by ≥5 percent) in patients treated with givosiran compared to placebo included serum creatinine increase (15 percent), fatigue (10 percent), transaminase elevations (8 percent), and rash (6 percent). Permanent discontinuation occurred in one patient receiving givosiran due to elevated liver transaminases.

For more information on ENVISION (NCT03338816), please visit clinicaltrials.gov or contact media@alnylam.com.

*GIVLAARI was approved by the United States Food and Drug Administration on November 20, 2019 for the treatment of adults with AHP. It is also approved in other countries globally; specific indications vary by country/region.

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