ENVISION Clinical Trial Overview

*Givosiran is an RNA interference (RNAi) therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) approved in the US 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 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 to receive monthly subcutaneous injection of givosiran at either 2.5 mg/kg or 1.25 mg/kg. The OLE period is ongoing, with a final data readout at 30 months.

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. Additionally, daily worst scores for fatigue and nausea were measured, 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.
- 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.

6-Month DB Results

- Relative to placebo, treatment with givosiran resulted in a statistically significant and clinically meaningful mean reduction of 70 percent in the AAR.
- Improvements were observed in a number of secondary endpoints, including reductions in urinary ALA and PBG levels, days of intravenous hemin use and daily worst pain for patients with AIP (P=0.046 by post hoc Wilcoxon signed-rank test).
  - Certain secondary endpoints did not meet the prespecified criteria for statistical significance in hierarchical testing including daily worst scores for fatigue or nausea.
- Givosiran treatment led to favorable effects in exploratory endpoints related to use of analgesics (opioids and non-opioids), overall health status and daily functioning.
  - The percentage of patients with AIP using any analgesics (opioids) during the trial 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 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 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) and participating in social activities (35.1 percent vs. 7.9 percent). Patients receiving givosiran also reported disease impact on daily functioning, including doing household chores (35.1 percent vs. 5.3 percent) and exercising moderately (32.4 percent vs. 5.3 percent), as well as satisfaction with treatment (72.2 percent vs. 13.5 percent).

• The most common adverse events observed in the givosiran group (reported in ≥20 percent of patients) were nausea (27 percent) and injection site reactions (25 percent). Other adverse events seen more frequently (by greater than 5 percent) in patients treated with givosiran compared to placebo included rash (17 percent), serum creatinine increase (15 percent), transaminase elevations (13 percent) and fatigue (10 percent). Permanent discontinuation occurred in one patient receiving givosiran due to elevated liver transaminases.

12-Month OLE Results

• Givosiran: Givosiran Patients
  - Continued givosiran treatment during months 6-12 led to sustained AAR reduction with a median AAR of 0.0.
  - The proportion of study-defined attack-free patients increased from 50.0 percent in the DB period to 61.7 percent in the first 6 months of the OLE period.
  - Sustained lowering of ALA and PBG was accompanied by sustained reductions in hemin use, daily worst pain scores from baseline and ongoing improvements in patient-reported quality of life and ability to function.
• Placebo: Givosiran Crossover Patients
  - Patients who crossed over from placebo in the DB period to givosiran in the OLE period experienced a median reduction in AAR of 83 percent, similar to that experienced by givosiran patients in the DB period.
  - Placebo crossover patients had reductions in hemin use and daily worst pain scores in the OLE period that were comparable to reductions in givosiran patients during the DB period, as well as improvements in patient-reported quality of life.
• The safety profile of givosiran in the first 6 months of the OLE period was consistent with that observed in the DB period, and there were no new safety findings.

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. GIVLAARI is also approved in the European Union and Brazil.

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