Givosiran: Hemin Use

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SUMMARY

- In the ENVISION study, hemin prophylaxis was prohibited, and patients were required to discontinue hemin prophylaxis at least 4 days prior to screening.[1]
- Episodic use of hemin for the treatment for porphyria attack was allowed. If hemin was used for porphyria attacks, urine samples were collected and assessed 4 days after the patient's last hemin dose.[2]
- At 6 months in the double-blind period of the ENVISION study, the mean annualized number of days of hemin use in patients with AIP was significantly lower in the givosiran group than in the placebo group.[1]
- During the ENVISION OLE period, the median annualized days of hemin use remained low in the continuous givosiran group and decreased by 97% in the placebo crossover group.[3]

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CLINICAL DATA

ENVISION Study

Study Design

The ENVISION study was a randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients (N=94) with a documented diagnosis of AHP. After the 6-month double-blind placebo-controlled period, all patients received givosiran treatment in the 30-month OLE period. The primary endpoint of the ENVISION double-blind period was the annualized rate of composite porphyria attacks defined as those requiring hospitalization, urgent healthcare visit, or IV hemin administration at home, in patients with AIP over the 6-month treatment period.[1]

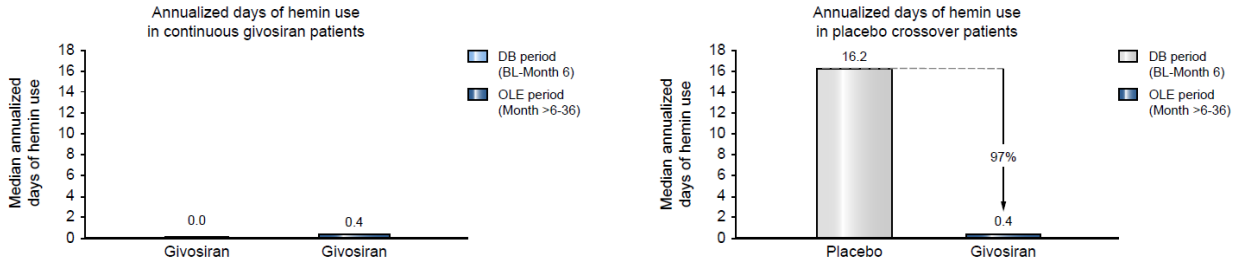
Hemin prophylaxis was prohibited in the ENVISION study, and patients were required to discontinue hemin prophylaxis at least 4 days prior to screening. Episodic use of hemin for the treatment of acute or ongoing porphyria attacks was allowed during the study.[2]

Hemin Use

At 6 months in the double-blind period of the ENVISION study, the mean annualized number of days of hemin use in patients with AIP was 77% lower ($p<0.001$) in the givosiran group (6.8 days) than in the placebo group (29.7 days).[1]

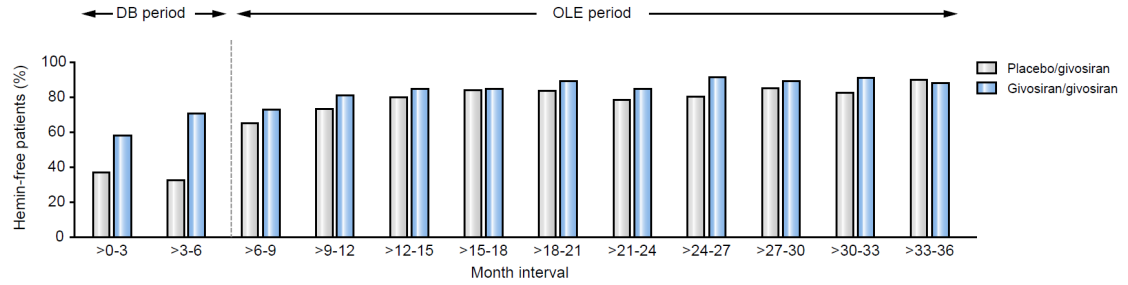
Median annualized days of hemin use remained low in the continuous givosiran group during the OLE period and decreased by 97% in the placebo crossover group during the OLE period (**Figure 1**). The proportion of patients with no days of hemin use increased over time in both the continuous givosiran and placebo crossover groups. Of the patients in the continuous givosiran group, 88% had no days of hemin use at >33–36 months. Of the patients in the placebo crossover group, 90% had no days of hemin use at >33-36 months (**Figure 2**).[3]

Figure 1. Median Annualized Days of Hemin Use: (Right) Continuous Givosiran and (Left) Placebo Crossover.[3]



Adapted from Kuter et al.[3]

Figure 2. Proportion of Patients with 0 Days of Hemin Use by 3-Month Interval.[3]



No. of patients												
Placebo/givosiran	46	46	46	45	45	44	43	42	41	40	40	39
Givosiran/givosiran	48	48	48	47	46	46	46	46	46	46	45	43

Adapted from Kuter et al.[3]

No additional data are available regarding the use of hemin during treatment with givosiran.

Safety Results

The safety profile of givosiran was evaluated in all patients. Median (range) exposure to givosiran was 33.1 (2.7–34.1) months for the continuous givosiran group and 27.7 (1.8–28.3) months for the placebo crossover group. The maximum exposure time to givosiran was 34.1 months.[4]

The majority of AEs were mild or moderate in severity, and a summary of adverse events is shown in **Table 1**. The most common AEs included injection-site reactions (39%), nausea (37%), fatigue (27%), and nasopharyngitis (27%). Overall, 4 patients discontinued givosiran treatment due to treatment-related AEs (blood homocysteine increase with concomitant injection-site reaction, blood homocysteine increase with concomitant pancreatitis, abnormal liver function test, and drug hypersensitivity). SAEs considered related to givosiran included increased blood homocysteine, elevated transaminases, retinal vein occlusion, injection-site reaction, pancreatitis, worsening of chronic renal failure, pulmonary embolism, right iliac thrombophlebitis, and worsening of liver tests. There was 1 death due to aortic dissection during the OLE period that was determined to be unrelated to givosiran.[3]

Table 1. Summary of Patient with ≥1 Adverse Event.[3]

Patients with ≥1 Event, n (%)	Placebo Crossover (N=46)	Continuous Givosiran (N=48)	All Patients (N=94)
Any AE	44 (96)	47 (98)	91 (97)
SAE	17 (37)	20 (42)	37 (39)
Severe AE	18 (39)	17 (35)	35 (37)
AE leading to treatment discontinuation	4 (9)	2 (4)	6 (6)
AE leading to study withdrawal	2 (4)	2 (4)	4 (4)
Death	0	1 (2)	1 (1)

AE, adverse event; SAE, serious adverse event.
Safety data from first dose of givosiran to completion of study, May 31, 2021

GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following section(s) of the GIVLAARI Prescribing Information[5]:

- CONTRAINDICATIONS Section 4

ABBREVIATIONS

AE = adverse event; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; DB = double-blind; OLE = open-label extension; SAE = serious adverse event.

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REFERENCES

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2. Supplement to: Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N Engl J Med*. 2020;382(24):2289-2301. doi:10.1056/NEJMoa1807838
3. Kuter DJ, Bonkovsky HL, Monroy S, et al. Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial. *J Hepatol*. 2023;79(5):1150-1158. doi:10.1016/j.jhep.2023.06.013
4. Kuter DJ, Bonkovsky HL, Monroy S, et al. Efficacy and safety of givosiran in patients with acute hepatic porphyria: 36-month results of the phase 3 ENVISION randomized clinical trial. Presented at: American Society of Hematology (ASH) Congress; December 11-14, 2021; Atlanta, GA, USA & Virtual.
5. GIVLAARI (givosiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.