Givosiran: Use in Patients with Prior History of Hemin Prophylaxis

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SUMMARY

- The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. The use of hemin prophylaxis was prohibited but may be given to treat acute attacks if clinically indicated, and patients were required to discontinue hemin prophylaxis at least 4 days prior to screening.[1,2]
- A post-hoc analysis of the ENVISION study was conducted to evaluate the treatment outcomes of givosiran in patients with or without prior hemin prophylaxis.[3]
  - Treatment with givosiran resulted in reductions in median AAR, regardless of prior hemin prophylaxis status.[3]
  - Increases in mean SF-12 PCS and MCS scores from baseline to the end of the double-blind and OLE periods were observed in the continuous-givosiran and placebo-crossover groups, regardless of prior hemin prophylaxis status.[3]
    - At 36 months of the ENVISION OLE, the majority of AEs were mild or moderate in severity. The most common AEs included injection-site reactions (39%), nausea (37%), and fatigue (27%).[1]

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STUDY DESIGN

The ENVISION study was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. Enrolled patients were randomized on a 1:1 basis to receive subcutaneous injections of givosiran 2.5 mg/kg (n=48) or placebo (n=46) once a month for 6 months, followed by an optional 30-month OLE. The primary endpoint was the annualized rate of composite porphyria attacks among patients with AIP at 6 months.[1]

Per the study protocol, the use of hemin prophylaxis was prohibited, 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] A post-hoc analysis of the ENVISION study was conducted to evaluate the treatment outcomes of givosiran in patients with or without prior hemin prophylaxis.[1,3]

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Ninety-four patients were enrolled in the 6-month double-blind period, and 93 patients entered the OLE period. The median (range) duration of historical hemin use was 5 (1-33) years. The baseline demographic and clinical characteristics by prior hemin prophylaxis use are presented in **Table 1**.[3,4]

Table 1. Patient Demographics and Baseline Characteristics by Prior Hemin Prophylaxis Status in ENVISION.[4]

Characteristic	Prior Hemin Prophylaxis			No Prior Hemin Prophylaxis		
	Placebo (n=18)	Givosiran (n=20)	Overall (n=38)	Placebo (n=28)	Givosiran (n=28)	Overall (n=56)
Age at diagnosis, years, median (range)	29.6 (17-44)	32.4 (16-48)	30.6 (16-48)	28.0 (18-51)	28.1 (5-58)	28.1 (5-58)
Years since diagnosis, median (range)	7.08 (0.7-38.5)	6.56 (0.2-35.3)	6.81 (0.2-38.5)	4.06 (0.1-25.0)	7.20 (0.4-43.3)	5.68 (0.1-43.3)
Historical AAR, median (range)[a]	9.0 (4-38)	9.0 (4-32)	9.0 (4-38)	6.0 (0-46)	8.0 (4-34)	7.0 (0-46)
Prior chronic symptoms, n (%)[b]	9 (50)	7 (35)	16 (42)	17 (61)	16 (57)	33 (59)
Prior chronic opioid use, n (%)[c]	6 (33)	8 (40)	14 (37)	7 (25)	6 (21)	13 (23)
Baseline urinary ALA (mmol/mol Cr), median (range)[d]	17.6 (4.1–36.8)	14.8 (1.8–88.9)	16.1 (1.8–88.9)	14.9 (0.7–42.7)	17.2 (2.8–37.3)	15.7 (0.7–42.7)
Baseline urinary PBG (mmol/mol Cr), median (range)[e]	54.5 (7.9–96.1)	37.3 (3.0–150.0)	40.7 (3.0–150.0)	32.6 (0.4–106.5)	45.6 (0.4–143.6)	40.3 (0.4–143.6)

Abbreviations: AAR = annualized attack rate; ALA = delta-aminolevulinic acid; Cr = creatinine; IV = intravenous; PBG = porphobilinogen; ULN = upper limit of normal.

[a]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home during the 6 months before randomization.

[b]Symptoms were chronic if patients experienced symptoms daily or on most days when not having an attack and were reported by investigators.

[c]Opioid use was defined as chronic if patients reported taking opioids for porphyria daily or most days when not having an attack.

[d]ALA reference range (ULN, 1.47 mmol/mol Cr).

[e]PBG reference range (ULN, 0.14 mmol/mol Cr).

EFFICACY RESULTS

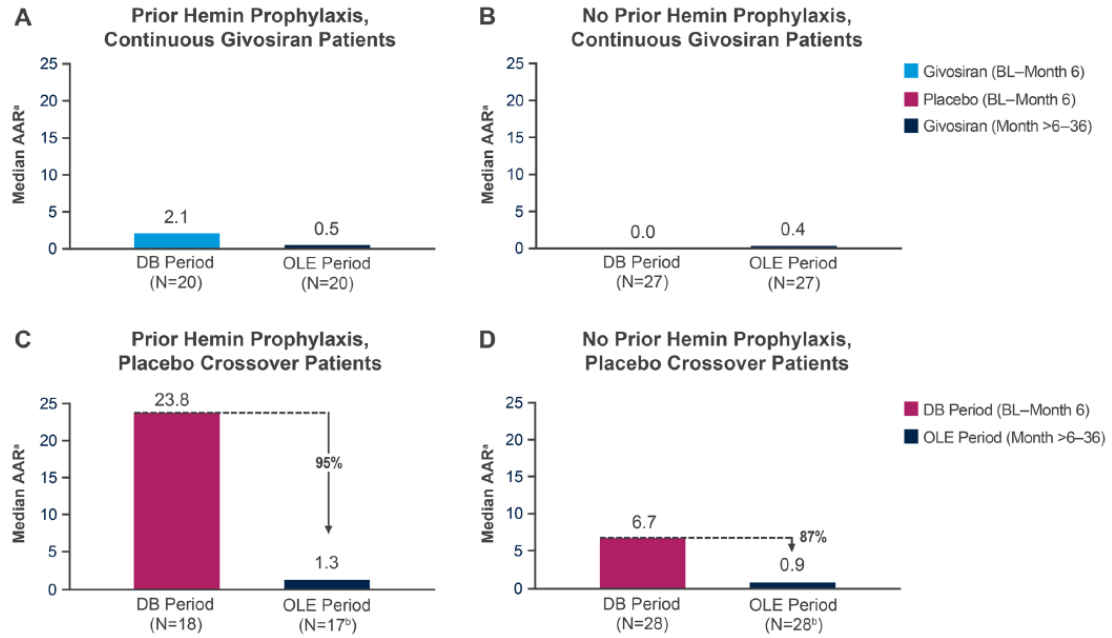
Attack Rate

During the 6-month double-blind period, the median AAR for patients treated with givosiran was 2.1 in those with prior hemin prophylaxis (n=20) and 0 in those without hemin prophylaxis (n=27). The median

AAR for patients treated with placebo was 23.8 in those with prior hemin prophylaxis (n=18) and 6.7 in those without (n=28) prior hemin prophylaxis.[3]

During the OLE period, a sustained reduction in median AAR was observed in continuous-givosiran group, regardless of prior hemin prophylaxis status. Furthermore, a reduction in median AAR was observed in the placebo-crossover group, regardless of prior hemin prophylaxis status (**Figure 1**).[3]

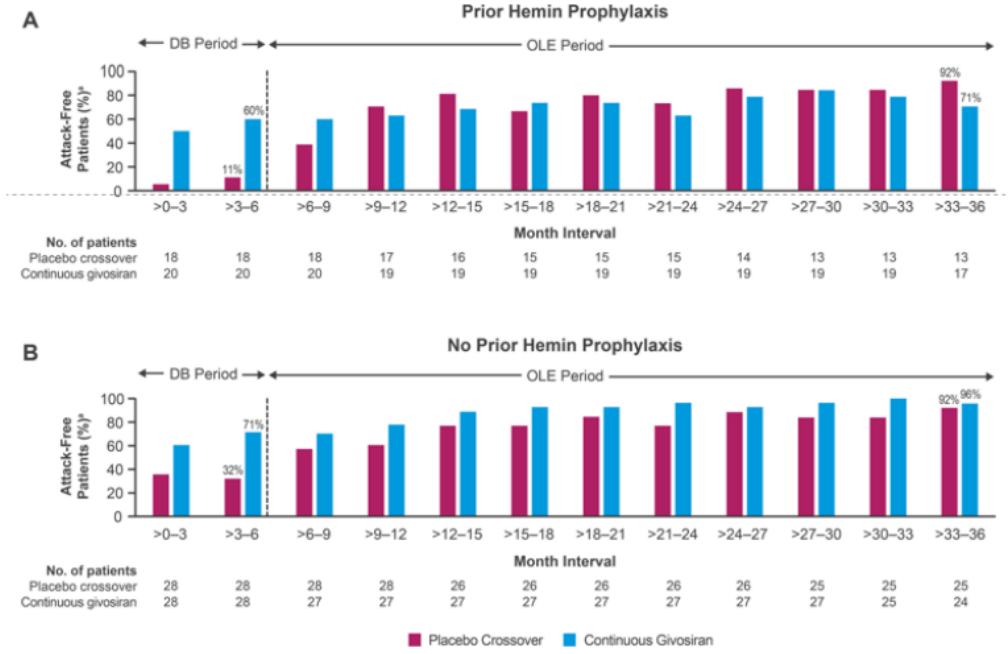
Figure 1. Median AAR for DB and OLE periods, by Treatment and Prior Hemin Prophylaxis Status.[3]



Abbreviations: AAR = annualized attack rate; BL = baseline; DB = double-blind; OLE = open-label extension
[a]Descriptive statistics.
[b]One patient with <85 days follow-up after taking givosiran was excluded from descriptive summaries.
From Deering et al.[3]

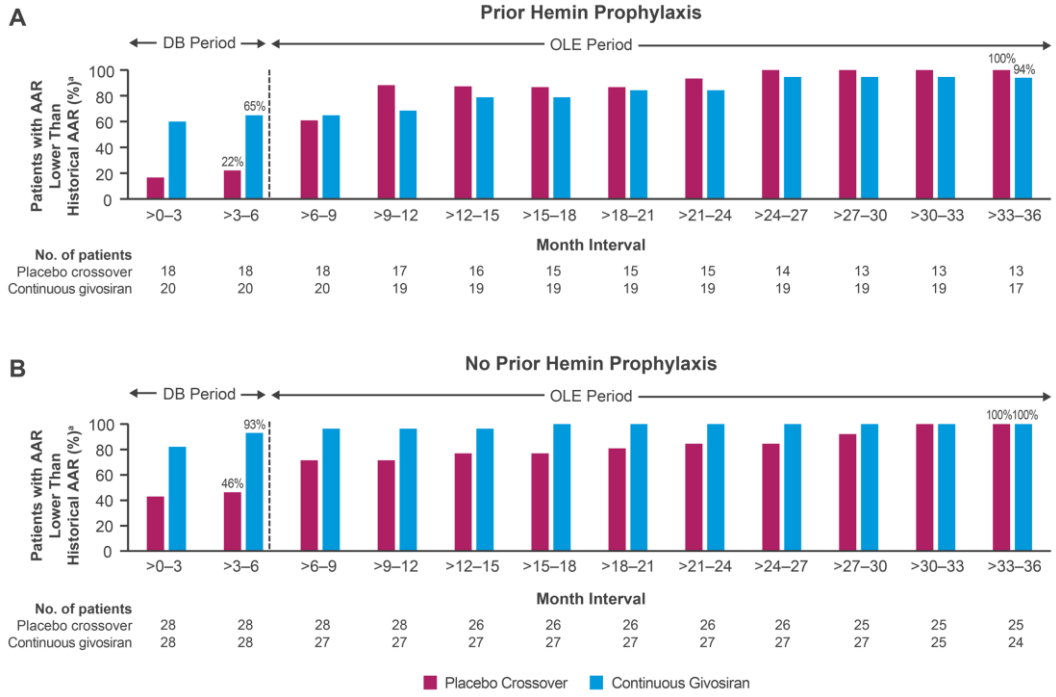
Regardless of prior hemin prophylaxis, the proportion of attack-free patients (**Figure 2**) and the proportion of patients whose AAR was lower and remained lower than the historical AAR (**Figure 3**) increased from the double-blind period through the OLE period in both treatment groups.[3]

Figure 2. Proportion of Attack-Free Patients, by 3-Month Interval, Treatment, and Prior Hemin Prophylaxis Status.[3]



Abbreviations: DB = double-blind; OLE = open-label extension.
[a]Descriptive statistics
From Deering et al.[3]

Figure 3. Proportion of Patients with an AAR That Was Lower Than the Historical AAR and Remained Lower, by 3-Month Interval, Treatment, and Prior Hemin Prophylaxis Status.[3]



Abbreviations: DB = double-blind; OLE = open-label extension.
[a]Descriptive statistics
From Deering et al.[3]

In the continuous-givosiran group, the estimated median (95% CI) time to first attack was 95.5 (8, not estimated) and 264 (37, not estimated) days in those with and without prior hemin prophylaxis, respectively. In the placebo-crossover group, the estimated median (95% CI) time to first attack was 7.5 (5, 10) and 41.5 (18, 104) days in those with and without prior hemin prophylaxis, respectively.[3]

Patient-Reported Quality of Life

Increases in mean SF-12 PCS and MCS scores were observed from baseline to the end of the double-blind and OLE periods in both treatment groups, regardless of prior hemin prophylaxis status (**Table 2**).[3]

Table 2. Mean Change from Baseline in SF-12 Summaries by Treatment and Prior Hemin Prophylaxis Status.[3]

	Prior Hemin Prophylaxis		No Prior Hemin Prophylaxis	
	Continuous Givosiran	Placebo Crossover	Continuous Givosiran	Placebo Crossover
Mean Change from Baseline in PCS				
At Month 6	3.4	0.3	6.4	2.7
At Month 36	8.7	11.3	8.6	8.4
Mean Change from Baseline in MCS				
At Month 6	6.1	1.6	1.7	-0.4
At Month 36	5.9	5.6	10.0	2.0

Abbreviations: MCS = mental component summary; PCS = physical component summary; SF-12 = 12-item Short Form Health Survey.

SAFETY

The safety results of givosiran for the subgroup of patients with prior hemin prophylaxis status are not available. The majority of AEs were mild or moderate in severity, and a summary of AEs is shown in **Table 3**. The most common AEs included injection-site reactions (39%), nausea (37%), and fatigue (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.[1]

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

Patients with ≥1 Event, n (%)	Placebo Crossover (n=46)	Continuous Givosiran (n=48)	All Patients (n=94)
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)

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

ABBREVIATIONS

AAR = annualized attack rate; AE = adverse event; AHP = acute hepatic porphyria; AIP = acute intermittent porphyria; ALA = delta-aminolevulinic acid BL = baseline; CI = confidence interval; Cr = creatinine; DB = double-blind; IV = intravenous; MCS = mental component summary; OLE = open-label extension; PBG = porphobilinogen; PCS = physical component summary; SAE = serious adverse event; SF-12 = 12-item Short Form Health Survey; ULN = upper limit of normal.

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