Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyria: 24-Month Interim Analysis of the Phase 3 ENVISION Randomized Clinical Trial

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Conclusions

- The ENVISION 24-month interim analysis further confirms that long-term dosing with givosiran provides sustained and continuous benefit to patients with AHP
- Long-term givosiran use demonstrated a durable response with efficacy across a wide range of clinical parameters during the OLE period
  - 83% and 76% of patients in the continuous givosiran and placebo crossover groups, respectively, continued to be attack-free during Months 21–24
  - The analysis showed a sustained reduction in AAR, ALA, and PBG levels, and hemin use and further improvements in physical functioning and QoL
- The safety profile of givosiran remained acceptable

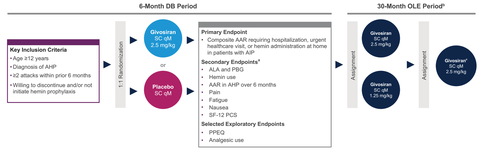
Background

- AHP is caused by hepatic heme biosynthesis defects leading to accumulation of neurotoxic heme intermediates, ALA and PBG, and/or porphyrins primarily in the liver[1-3]
- AHP is characterized by acute disabling and sometimes life-threatening neurovisceral attacks manifesting as severe abdominal pain, which can become recurrent in some patients[4,5]
- Givosiran, a subcutaneously administered RNA interference therapeutic that specifically targets ALAS1 mRNA in the liver to reduce ALA and PBG,[6] is approved for treatment of AHP in adults in the United States and adults and adolescents aged 12 years or older in the European Union[7,8]
- During the 6-month DB period of the ENVISION study (NCT03338816), givosiran treatment reduced AAR by 74% and reduced ALA and PBG levels, hemin use, and daily pain versus placebo[9]
- Data from the 24-month interim analysis of the OLE of ENVISION are reported

Methods

- The ENVISION study design is shown in **Figure 1**

Figure 1. ENVISION Study Design



[a]Endpoints were evaluated in patients with genetically confirmed AIP (except where noted otherwise) at 6 months. [b]For the OLE period, all endpoints were exploratory. [c]A protocol amendment increased the dose to 2.5 mg/kg monthly for all patients.

Results

Table 1. Baseline Demographics and Disease Characteristics

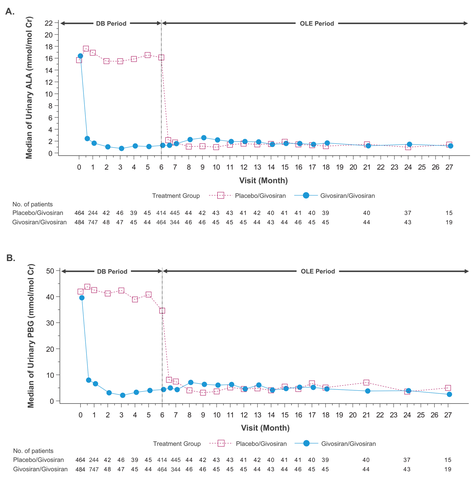
Demographic/Characteristic	Placebo–Givosiran Crossover (n=46)	Continuous Givosiran (n=48)	All Patients Who Received Givosiran (N=94)
Age at screening, y, median (range)	36 (20–60)	42 (19–65)	38 (19–65)
Female, n (%)	41 (89)	43 (90)	84 (89)
AIP with identified mutation, n (%)	43 (94)	46 (96)	89 (95)
Years since diagnosis, median (range)	6.5 (0.1–38.5)	7.0 (0.2–43.3)	6.6 (0.1–43.3)
Prior hemin prophylaxis, n (%)	18 (39)	20 (42)	38 (40)
Historical AAR,[a] median (range)	7.0 (0[b]–46)	8.0 (4–34)	8.0 (0[b]–46)
Chronic symptoms daily or most days between attacks, n (%)	26 (57)	23 (48)	49 (52)
Baseline urinary ALA, mmol/mol Cr, median (range)	16.4 (1.4–41.5)	16.4 (1.8–88.9)	16.4 (1.4–88.9)
Baseline urinary PBG, mmol/mol Cr, median (range)	39.3 (3.6–87.7)	39.6 (0.4–150.0)	39.6 (0.4–150.0)

[a]Composite porphyria attacks requiring hospitalization, an urgent health care facility visit, or IV hemin treatment at home. [b]One patient in the placebo group was enrolled in the study but did not meet an inclusion criterion (did not have requisite number of attacks within 6 months before randomization). Reference ranges: ALA (0.09–3.0 mmol/mol Cr; ULN, 1.47 mmol/mol Cr), PBG (0.0–1.1 mmol/mol Cr; ULN, 0.137 mmol/mol Cr).[3]

- Ninety-four patients with AHP were enrolled at 36 sites in 18 countries
- All patients completed the 6-month DB period, and all eligible patients (n=93) entered the 30-month OLE period
- Baseline characteristics were generally balanced between groups (**Table 1**)

ALA and PBG Levels

Figure 2. Median Levels of Urinary ALA (A) and PBG (B) during DB and OLE Study Periods[a]

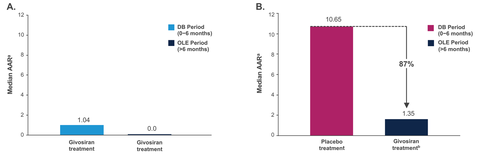


[a]OLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled.
Reference ranges: ALA (0.09–3.0 mmol/mol Cr; ULN, 1.47 mmol/mol Cr), PBG (0.0–1.1 mmol/mol Cr; ULN, 0.137 mmol/mol Cr).[3]

- In the placebo–givosiran crossover and continuous givosiran groups, givosiran treatment led to sustained lowering of median ALA levels to near normal and to lowering of PBG levels by >75% through Month 24 (**Figure 2**)

Attacks

Figure 3. Median AAR for DB and OLE Study Periods: (A) Continuous Givosiran and (B) Placebo Crossover

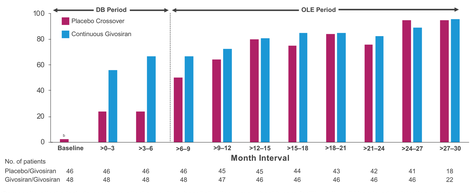


[a]Descriptive analysis. [b]Placebo crossover patients receiving givosiran 2.5 mg/kg (n=29) or 1.25 mg/kg (n=17).

Continued givosiran treatment during the OLE period led to a sustained reduction in AAR (**Figure 3**)

- After the initial 6-month DB period, the median number of attacks during the OLE period (Month 6 to Month 24 data cutoff) was 0 and 1.35 in the continuous givosiran and placebo crossover groups, respectively

Figure 4. Proportion of Composite Attack–Free Patients by 3-Month Interval during DB and OLE Periods[a]

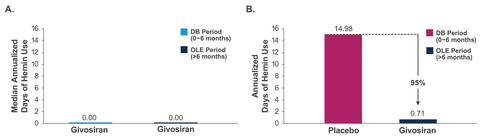


[a]Composite attacks include porphyria attacks requiring hospitalization, urgent health care facility visit, or IV hemin administration at home; 1 month = 28 days. [b]Baseline represents 6 months before randomization.

- The proportion of patients with no attacks by 3-month interval improved with continued givosiran treatment during the OLE period (**Figure 4**)
  - 83% of patients who continued givosiran treatment were attack-free at >21−24 months
  - 76% of patients who crossed over from placebo to givosiran were attack-free at >21−24 months
    - In comparison, 24% of those who received placebo were attack-free at >3−6 months of the DB period

Hemin Use

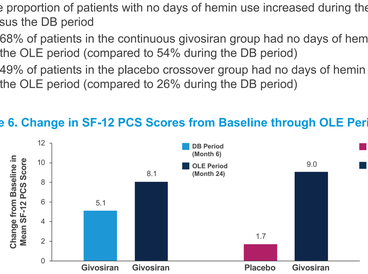
Figure 5. Median Annualized Days of Hemin Use: (A) Continuous Givosiran and (B) Placebo Crossover



- Median annualized days of hemin use remained at 0 in the continuous givosiran group during the OLE period and decreased by 95% in the placebo crossover group during the OLE period (**Figure 5**)
- The proportion of patients with no days of hemin use increased during the OLE period versus the DB period
  - 68% of patients in the continuous givosiran group had no days of hemin use during the OLE period (compared to 54% during the DB period)
  - 49% of patients in the placebo crossover group had no days of hemin use during the OLE period (compared to 26% during the DB period)

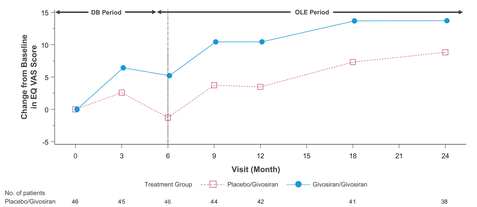
QOL

Figure 6. Change in SF-12 PCS Scores from Baseline through OLE Period[a]



[a]Estimates for the clinically meaningful difference are ≥2 to 5 points for SF-12 PCS, based on published data for other chronic diseases.[10,11]

Figure 7. Change in EQ-VAS Scores from Baseline through OLE Period[a]

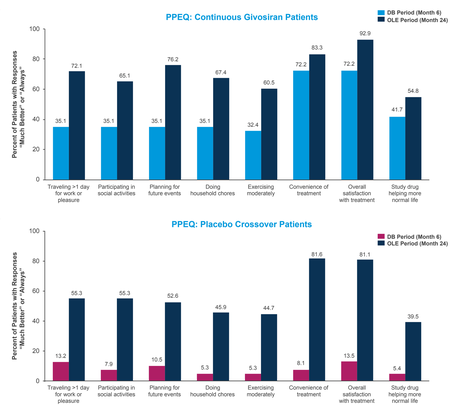


[a]Estimates for the clinically meaningful difference are ≥7 to 8 points for EQ-VAS, based on published data for other chronic diseases.[12,13]

- With givosiran, patients experienced further improvements in QOL, as assessed with SF-12 PCS scores (**Figure 6**) and EQ-VAS scores (**Figure 7**)
  - Improvements in QOL scores were sustained from Month 6 to Month 24 in patients who continued givosiran treatment
  - At Month 24, similar improvements were observed in patients who crossed over from placebo to givosiran

Patient-Reported Outcomes

Figure 8. Percentage of Patients Who Reported Ability Improvements ("Much Better" or "Always") on PPEQ: (A) Continuous Givosiran and (B) Placebo Crossover



- From the DB period through the OLE period, PPEQ results showed further improvements across all domains, including activities of daily living, satisfaction with treatment, and living a more normal life, in patients who continued givosiran (**Figure 8**)
  - Improvements across all domains were also observed from the DB period through the OLE period in patients who crossed over from placebo to givosiran

Safety

Table 2. Summary of Adverse Events[a]

≥1 Event, n (%)[a]	Placebo–Givosiran Crossover (n=46)	Continuous Givosiran (n=48)	All Patients Who Received Givosiran (N=94)
AE	43 (94)	47 (98)	90 (96)
SAE[b]	13 (28)	15 (31)	28 (30)
Severe AE	14 (30)	13 (27)	27 (29)
AE leading to treatment discontinuation	2 (4)	1 (2)	3 (3)
AE leading to study withdrawal	2 (4)	1 (2)	3 (3)
Death	0	0	0

[a]Safety data from first dose of givosiran to data cutoff date, June 24, 2020. [b]SAE of liver function test abnormal that led to treatment discontinuation during DB period was previously reported.[3]

- Median (range) exposure was 24.2 (2.7–30.4) months for the continuous givosiran group and 18.8 (1.8–24.7) months for the placebo crossover group, with maximum exposure of 30.4 months; for calculating exposure, 1 month = 30.44 days
- The safety profile of givosiran remained acceptable with long-term treatment (**Table 2**)
- The majority of AEs continued to be mild or moderate in severity
- Overall, the most common AEs (≥20% of patients) were injection-site reactions (37% [35/94]), nausea (34% [32/94]), fatigue (23% [22/94]), nasopharyngitis (23% [22/94]), and headache (20% [19/94])
  - The most common treatment-related AEs (≥10% of patients) were injection-site reactions (29% [27/94] patients), nausea (20% [19/94]), and fatigue (13% [12/94])
  - Three treatment-related AEs led to withdrawal from the study (blood homocysteine increases, 2 patients; abnormal liver function test, 1 patient)
- SAEs that occurred in ≥2% of patients included blood homocysteine increased, chronic kidney disease, device breakage, pyrexia, and urinary tract infection (each occurred in 2 patients)
- There were no deaths
- Hepatic AEs were reported in 17 (18%) patients; all were mild to moderate in severity
  - ALT elevations were reported in 8 (9%) patients and AST elevations in 6 (6%) patients
- Renal AEs (mostly increased blood creatinine and/or decreased eGFR) were reported in 21 (22%) patients; none led to discontinuation of treatment

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Abbreviations: AAR, annualized attack rate; AE, adverse event; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; DB, double-blind; eGFR, estimated glomerular filtration rate; EQ-VAS, EuroQol visual analog scale; IV, intravenous; mRNA, messenger ribonucleic acid; OLE, open-label extension; PBG, porphobilinogen; PCS, Physical Component Summary; PPEQ, Porphyria Patient Experience Questionnaire; qM, every month; QOL, quality of life; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; SF-12, Short Form (12-item) Health Survey

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