Twelve-Month Interim Analysis of Efficacy and Safety of Givosiran, an Investigational RNAi Therapeutic for Acute Hepatic Porphyria, in the ENVISION Open-Label Extension

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Acute Hepatic Porphyria (AHP)

Disease Overview
- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in the liver[1,2]
- Acute intermittent porphyria (AIP) is the most common type of AHP[3,4]
- ALAS1 induction leads to accumulation of toxic intermediates ALA/PBG, thought to cause AHP manifestations[1,2,5]

Attacks, Chronic Manifestations, and Comorbidities
- Acute neurovisceral attacks commonly manifest as severe abdominal pain and can be life-threatening[6,7]
- Chronic debilitating symptoms can negatively impact daily functioning and quality of life (QOL)[6–8]
- Comorbidities include hypertension, chronic kidney disease, and liver disease[3,6,9–11]

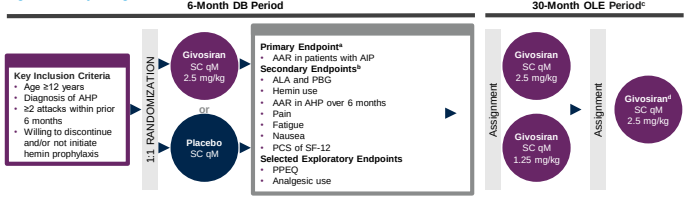
Unmet Need
- Hemin used to treat acute attacks and sometimes as off-label treatment to prevent attacks[7]
- Unmet need for therapies to prevent attacks and chronic disease manifestations

Givosiran
- Subcutaneously administered RNAi therapeutic that specifically targets ALAS1 messenger RNA in the liver to reduce disease-causing neurotoxic intermediates ALA and PBG
- Approved for treatment of AHP in adults in the US and adults and adolescents aged 12 years or older in the EU[12,13]

Methods

- 94 patients with AHP enrolled in ENVISION at 36 sites in 18 countries
- All patients completed the 6-month double-blind (DB) period; all eligible patients (n=93) entered the 30-month open-label extension (OLE) period (**Figure 1**); here we present results from a 12-month interim analysis

Figure 1. Study Design



[a]Composite annualized attacks requiring hospitalization, urgent healthcare visit, or hemin administration at home. [b]Endpoints evaluated in patients with genetically confirmed AIP, unless otherwise noted, at 6 months. [c]All endpoints listed above were considered exploratory in the OLE period. [d]A protocol amendment increased the dose of all patients to 2.5 mg/kg monthly

Results

- Baseline characteristics were generally balanced between groups (**Table 1**)

Table 1. Demographics and Baseline Characteristics of Patients in ENVISION

Characteristic	Placebo Crossover (N=46)	Givosiran (N=48)
Age at screening, years, median (range)	36 (20, 60)	42 (19, 65)
Female, n (%)	41 (89)	43 (90)
Years since diagnosis, median (range)	6.46 (0.1, 38.5)	6.98 (0.2, 43.3)
Prior hemin prophylaxis, n (%)	18 (39)	20 (42)
Historical AAR[a], median (range)	7.0 (0^b, 46)	8.0 (4, 34)
Chronic symptoms daily or most days between attacks, n (%)	26 (57)	23 (48)
Opioid use daily or most days between attacks, n (%)	13 (28)	14 (29)
Baseline urinary ALA (mmol/mol Cr), median (range)	16.4 (1.4, 41.5)	16.4 (1.8, 88.9)
Baseline urinary PBG (mmol/mol Cr), median (range)	39.3 (3.6, 87.7)	39.6 (0.4, 150.0)

[a]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home. [b]One patient in the placebo group did not meet inclusion criterion of ≥2 attacks requiring hospitalization, urgent healthcare visit, or IV hemin at home within 6 months prior to screening (patient had 2 attacks that were treated at home without IV hemin). This was identified as a protocol deviation

Givosiran Treatment Led to Sustained and Rapid Reduction of Attacks

- Continued givosiran treatment led to sustained reduction in attacks during the OLE (**Figure 2A and 3**)
- Placebo crossover patients had similar reduction in attacks during the OLE period as givosiran patients in the DB period (**Figure 2B and 3**)[a,14]
  - Trend toward increased efficacy in placebo crossover patients for 2.5 mg/kg[b] dose compared with 1.25 mg/kg[c] dose (intra-patient AAR reduction of 79% vs 67%, respectively)

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

Figure 2A. AAR in Givosiran Patients

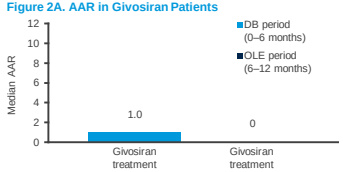


Figure 2B. AAR in Placebo Crossover Patients

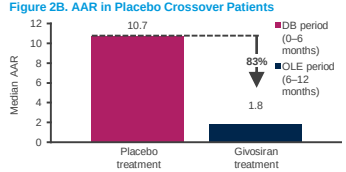
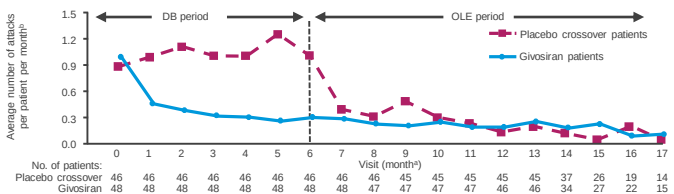


Figure 3. Average Number of Attacks over Time

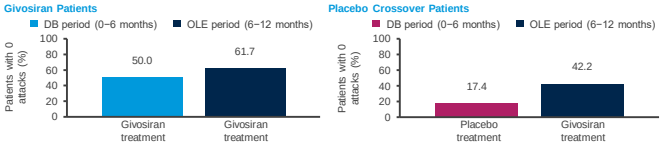


[a]Month = 28 days. [b]OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled

Increased Number of Patients with Zero Attacks with Long-Term Dosing

- Proportion of patients with zero attacks increased with continued givosiran treatment (givosiran patients) or with switch to givosiran (placebo crossover patients) in the OLE compared with the DB period (**Figure 4**)[14]

Figure 4. Proportion of Patients with Zero Attacks



Rapid and Sustained Lowering of ALA and PBG Levels with Long-Term Dosing

- During the OLE, givosiran treatment led to sustained (continuous givosiran patients) or rapid (placebo crossover patients) reductions in ALA and PBG levels (**Figure 5A and B**)

Figure 5A. Urinary ALA Levels over Time

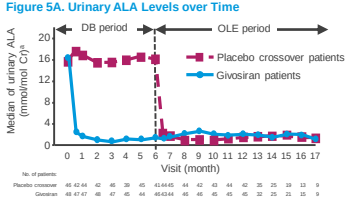
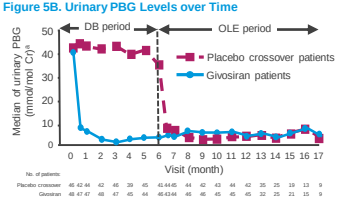


Figure 5B. Urinary PBG Levels over Time

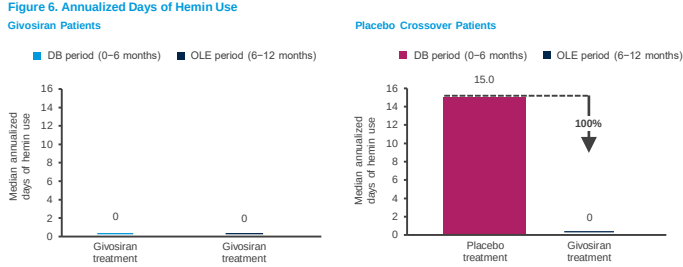


[a]OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled

Sustained Reductions in Hemin Use and Pain with Long-Term Dosing

- Continued givosiran treatment led to sustained reductions in hemin use in the OLE period, with 70% of patients requiring zero days of hemin
- Placebo crossover patients had 100% reduction in median annualized days of hemin use during the OLE period, consistent with data in givosiran patients during the DB period[15] (**Figure 6**)
- Givosiran treatment led to lower daily worst pain scores (reported by patients using a numeric rating score) in placebo crossover patients and further decreases for patients continuing givosiran compared with the DB period[14]

Figure 6. Annualized Days of Hemin Use



Improvement in QOL with Long-Term Dosing

- Givosiran treatment led to improvements in QOL, as demonstrated by higher SF-12 scores in placebo crossover patients and further improvements in patients continuing givosiran treatment compared with the DB period[14]
- A custom questionnaire assessing multiple life domains observed improvement in all domains in placebo crossover patients and further improvements in patients continuing givosiran treatment compared with the DB period[14]

Safety Profile of Givosiran Remained Acceptable with No New Safety Concerns

- Overall exposure: 11.22 months (median; range 1.8 to 19.5 months); cumulative exposure of 84.5 person-years[a]
- Incidence of AEs (placebo crossover vs givosiran): AEs, 91 vs 96%; SAEs, 13 vs 29%; severe AEs, 20 vs 23%
- Majority of AEs were mild or moderate in severity
- Most common related AEs (≥10%) were ISRs (33% of patients; 7.4% of injections), nausea, and fatigue
- SAEs in ≥2% were CKD and urinary tract infection (2 patients each)
- 1 patient discontinued treatment (described below), no other treatment discontinuations due to AEs; no deaths
- Safety profile was acceptable at both 2.5 mg/kg and 1.25 mg/kg doses

[a]For calculating exposure: 1 month=30.44 days

Hepatic Events in Patients with AHP

- Hepatic AEs were reported in 16 patients (17%)[a]; all were mild or moderate in severity
  - Majority were elevations of serum aminotransferases
- 1 patient with ALT >8×ULN discontinued treatment due to protocol-defined stopping rule in DB period
- ALT elevations generally occurred ~3 to 6 months after givosiran started and resolved

Renal Events in Patients with AHP

- 10 patients (11%) had renal AEs[b], characterized by increased serum creatinine and/or decreased eGFR
  - Majority of AEs mild or moderate in severity and none led to discontinuation of study treatment
- Mean eGFR was generally stable over time

[a]Hepatic AEs included any AEs within the Drug-related hepatic disorders Standardized MedDRA query. [b]Renal AEs included custom search for any AEs of blood creatinine increased, glomerular filtration rate decreased, CKD, nephropathy, renal impairment, and renal failure

ENVISION 12-Month OLE Summary

- Reductions in annualized rate of composite porphyria attacks and hemin use in patients with AHP were sustained or enhanced during the OLE
- Givosiran treatment led to sustained lowering of ALA and PBG levels through Month 12 in the OLE
- Givosiran treatment led to reductions in daily worst pain and improvements in QOL
- Safety profile of givosiran remained acceptable with no new safety findings identified

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Abbreviations: AAR, annualized rate of composite porphyria attacks; AE, adverse event; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; ALT, alanine aminotransaminase; Cr, creatinine; DB, double-blind; eGFR, estimated glomerular filtration rate; ISR, injection-site reaction; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; No., number; OLE, open-label extension; PBG, porphobilinogen; PCS, Physical Component Summary; PPEQ, Porphyria Patient Experience Questionnaire; qM, every month; QOL, quality of life; RNAi, RNA interference; SC, subcutaneous; SAE, serious adverse event; SF-12, Short Form (12-item) Health Survey; ULN, upper limit of normal

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