Overall Health, Daily Functioning, and Quality of Life in Patients with Acute Hepatic Porphyria: ENVISION, a Phase 3 Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Introduction

Acute Hepatic Porphyria (AHP)

- AHP is a family of rare, genetic diseases characterized by potentially life-threatening acute attacks and chronic manifestations that negatively impacting daily functioning and quality of life (QOL)[1–3]
- AHP is caused by a genetic mutation in 1 of 4 enzymes responsible for heme synthesis in liver[4,5]
- Upregulation of 5-aminolevulininic acid synthase 1 (ALAS1) is central to disease pathophysiology, leading to accumulation of toxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG) upstream of enzyme defects[5,6]
- Acute intermittent porphyria (AIP) is most common AHP type, with a mutation in *hydroxymethylbilane synthase (HMBS)* gene[1,4]
- Current treatment options for AHP patients experiencing ongoing attacks are limited and include avoidance of triggers, hormone suppression, intravenous (IV) hemin and in rare cases liver transplantation [7]

Givosiran

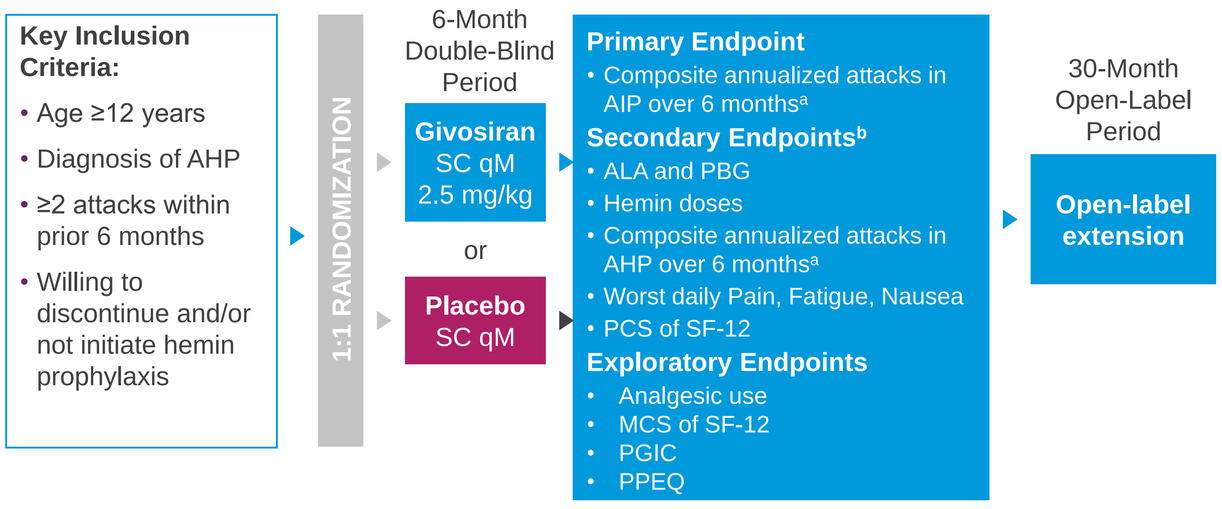
- Investigational RNAi therapeutic in development for the treatment of AHP
- Therapeutic hypothesis: Givosiran reduces hepatic ALAS1 mRNA protein levels, leading to sustained reductions in disease causal factors ALA and PBG

ENVISION Study Design (Figure 1)

- ENVISION (NCT03338816), a Phase 3, multicentre randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of givosiran in patients with AHP experiencing attacks
- Here we present patient-reported outcomes (PROs) from ENVISION; please see Gouya and Sardh et al (ICPP 2019) for oral presentations on ENVISION

Methods

Figure 1. ENVISION Study Design



[a]Attacks requiring hospitalization, urgent healthcare visit or at-home hemin administration; [b]Endpoints evaluated in genetically-confirmed AIP patients, unless otherwise noted.

- PRO measures and instruments selected based on literature review, EXPLORE natural history study and a qualitative patient interview study[8-10]:
  - **Pain –** Brief Pain Inventory-Short-Form Numeric Rating Scale (NRS), item #3 (pain at its worst in last 24 hours) captured daily by e-diary
  - **Fatigue –** Brief Fatigue Inventory-Short-Form NRS, item #3 (fatigue at its worst in last 24 hours) captured daily by e-diary
  - **Nausea –** 0 to 10 NRS scale (nausea at its worst in last 24 hours) captured daily by e-diary
  - **QOL –** Physical Component Summary (PCS) of the Short-Form (12-item) Health Survey version 2 (SF-12), 5-level EuroQoL 5 Dimensions Questionnaire visual analog scale (EQ-5D-5L VAS); Patient Work, School, and Caregiver Status Questionnaire
  - **Patient experience: global rating of change scales –** Patient Global Impression of Change (PGIC), Porphyria Patient Experience Questionnaire (PPEQ), Custom questionnaire that used global rating of change, with questions asked once at month 6, looking back at entire study period.
- Secondary endpoints were analyzed in a prespecified hierarchical order to control the overall type I error
- The population analyzed here included all randomized patients who received at least 1 dose of trial drug

Results

Trial Population

- Overall, 94 patients (from 36 trial sites in 18 countries) were enrolled and randomized to receive givosiran (n=48) or placebo (n=46)
- The majority of patients had AIP (n=89) and were female (n=84)
- Baseline demographics and disease characteristics for placebo- and givosiran-treated patients in the AIP subpopulation are summarized in (**Table 1)**

Table 1. Baseline Demographics and Characteristics of Patients

Characteristic	AIP Subpopulation	
	Placebo (n=43)	Givosiran (n=46)
Age, years, mean (SD)	37.3 (10.5)	40.7 (12.0)
Female, n (%)	39 (91)	41 (89)
Race, n (%)		
White	33 (77)	37 (80)
Black/African American	1 (2)	0 (0)
Asian	6 (14)	8 (17)
Other	3 (7)	1 (2)
BMI, kg/m^2	25.7 (6.3)	24.3 (5.2)
Region, n (%)[a]		
North America	17 (40)	16 (35)
Europe	18 (42)	22 (48)
Other	8 (19)	8 (17)
Time since diagnosis, years, mean (SD),	8.4 (8.7)	11.5 (11.3)
Prior hemin prophylaxis, n (%)	17 (40)	20 (43)
Prior AAR[b], median (range)	8 (0–46)	8 (4–34)
Prior chronic symptoms, n (%)	24 (56)	22 (48)
Prior chronic opioid use, n (%)	12 (28)	14 (30)
ALA levels, mean (SD)	17.5 (10.9)	20.0 (16.8)
PBG levels, mean (SD)	46.8 (24.3)	50.4 (34.3)
PCS of SF-12, mean (SD)[c]	38.4 (9.5)	39.4 (9.6)
MCS of SF-12, mean (SD)[c]	41.0 (10.1)	40.4 (8.1)
EQ-5D-5L VAS scores, mean (SD)[d]	65.7 (19.3)	62.7 (23.1)

[a]North America: USA, Mexico and Canada. Europe: Belgium, Bulgaria, Denmark, Finland, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden, Switzerland, and United Kingdom. "Other" includes Asia: Japan, South Korea and Taiwan and Oceania: Australia
[b]attacks requiring hospitalization, urgent healthcare visit, or IV hemin at home
[c]Both the PCS and MCS of SF-12 have a mean of 50 and a SD of 10 in the U.S. general population
[d]EQ-5D-5L VAS scores have a mean of 84 and a SD of 12.6 in the general population

Pain, Fatigue, and Nausea (AIP)

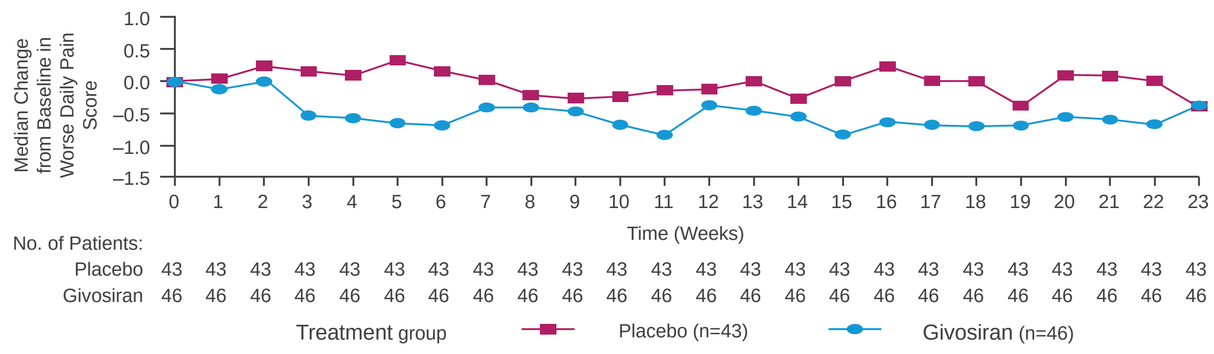
- Patients receiving Givosiran reduced daily worst pain scores compared with placebo over 6 months (p=0.046) (**Table 2**)
- Givosiran-treated patients experienced sustained improvements in pain from Week 1 (**Figure 2**); median treatment difference of –0.45 (p=0.049)
- Patients treated with givosiran had a reduction in opioid use over 6 months (mean proportion of days with opioid use 23% vs 38% for placebo)
- Differences in fatigue scores between givosiran and placebo groups were not significant; therefore, significance testing was not reported for nausea in accordance with the hierarchical statistical analysis of secondary endpoints (**Table 2**)

Table 2. PROs for Patients with AIP

PROs	Placebo (n=43)	Givosiran (n=46)	Treatment Difference (95% CI)	P-Value
Median daily worst pain, AUC[a,b]	5.3	–11.5	–10.1 (–22.8, 0.9)	0.046
Mean daily worst fatigue, AUC[b]	–4.2	–11.1	–6.9 (–19.8, 6.0)	0.288
Daily worst nausea, AUC[b]	–4.0	1.5	5.5 (–4.0, 15.0)	0.253

6-month AUC was calculated based on change from baseline in weekly mean scores
[a]Data were not normally distributed so a non-parametric stratified Wilcoxon test was used
[b]Negative, lower scores indicate a lowering of symptoms

Figure 2. Median Change from Baseline in Worst Daily Pain Score in Patients with AIP

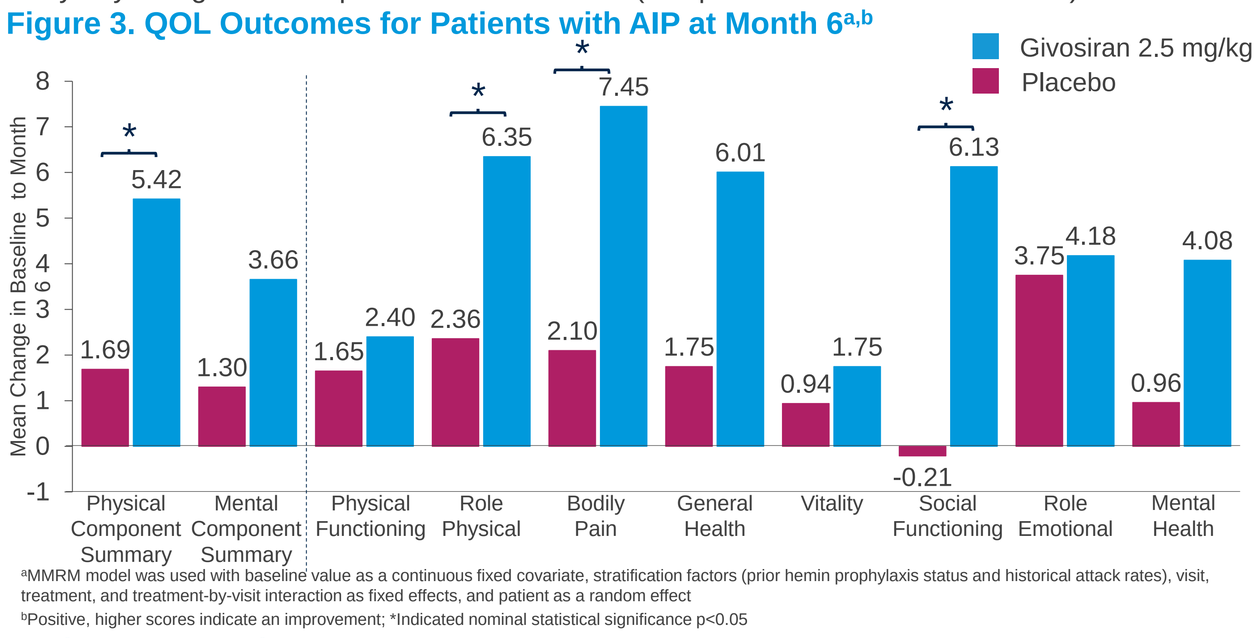


Assumptions on prespecified ANCOVA model, i.e., normality and constant variance of residuals, were checked with a normal Q-Q plot. Shapiro–Wilk normality test resulted in p-value of 0.0258, indicating significant deviation from normal distribution

QOL, Work Productivity, Caregiver Burden

- Clinically meaningful improvements in EQ-5D-5L VAS scores (5.2 vs -1.3), and PCS of SF-12 and MCS of SF-12 **(Figure 3),** based on published minimum clinically important difference values[11,12], were captured for givosiran-treated patients compared with placebo-treated patients
- 40 patients with AIP were employed at baseline, 20 in each treatment group; those treated with givosiran missed fewer days on average over 4 weeks (2.4) compared with placebo at Month 6 (6.9)
- At Month 6 givosiran treated AIP patient caregivers reported a mean number of hours assisted by any caregiver in the past week of 6.5 hours (compared to baseline of 13 hours)

Figure 3. QOL Outcomes for Patients with AIP at Month 6[a,b]

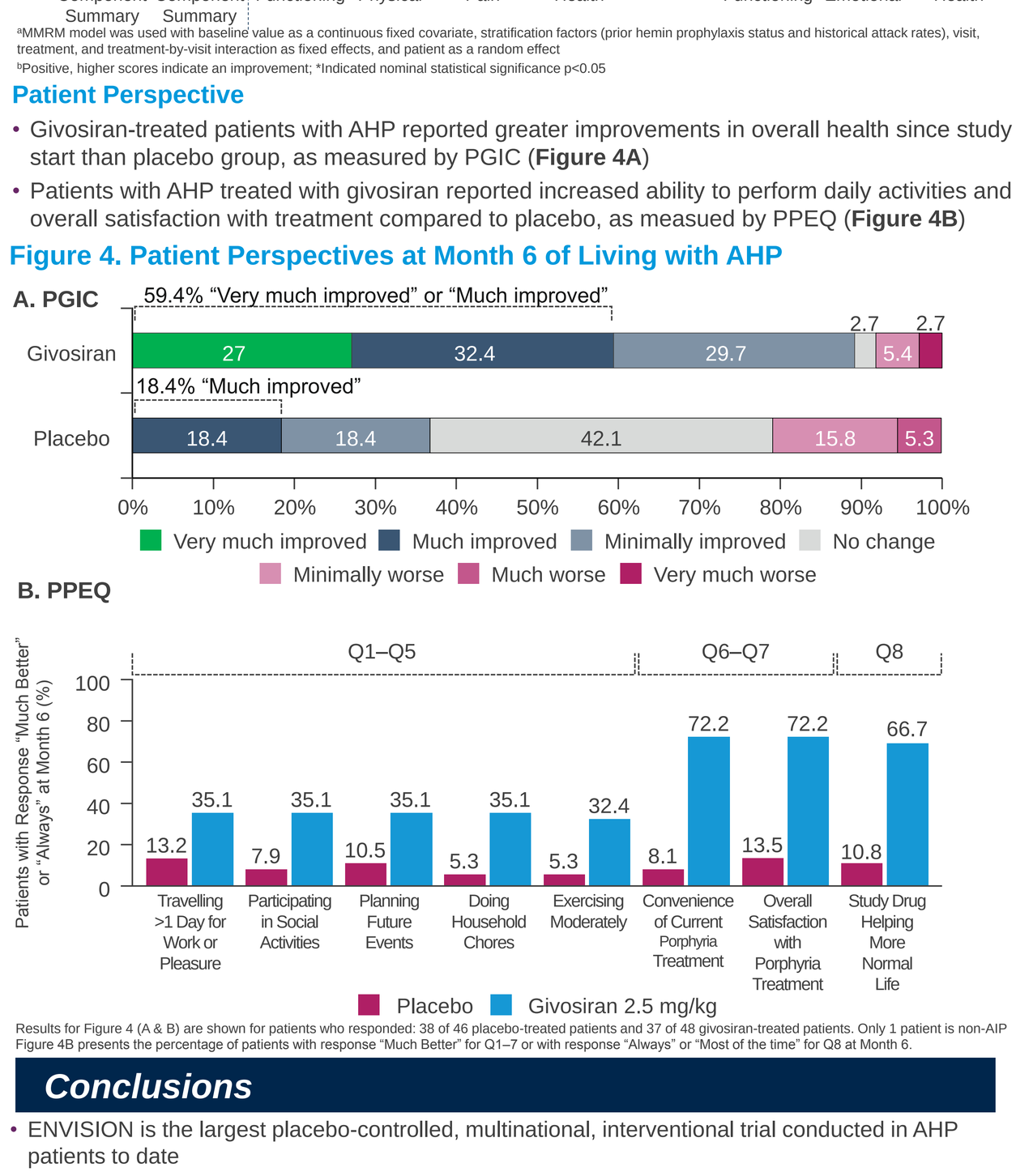


[a]MMRM model was used with baseline value as a continuous fixed covariate, stratification factors (prior hemin prophylaxis status and historical attack rates), visit, treatment, and treatment-by-visit interaction as fixed effects, and patient as a random effect
[b]Positive, higher scores indicate an improvement; *Indicated nominal statistical significance p<0.05

Patient Perspective

- Givosiran-treated patients with AHP reported greater improvements in overall health since study start than placebo group, as measured by PGIC (**Figure 4A**)
- Patients with AHP treated with givosiran reported increased ability to perform daily activities and overall satisfaction with treatment compared to placebo, as measued by PPEQ (**Figure 4B**)

Figure 4. Patient Perspectives at Month 6 of Living with AHP



Results for Figure 4 (A & B) are shown for patients who responded: 38 of 46 placebo-treated patients and 37 of 48 givosiran-treated patients. Only 1 patient is non-AIP
Figure 4B presents the percentage of patients with response "Much Better" for Q1–7 or with response "Always" or "Most of the time" for Q8 at Month 6.

Conclusions

- ENVISION is the largest placebo-controlled, multinational, interventional trial conducted in AHP patients to date
- Improvements in daily worst pain, a cardinal symptom of porphyria, along with decreased opioid use in givosiran-treated AIP patients were reported, as were improvements in SF-12 PCS and EQ-5D-5L VAS scores
- AHP patients receiving givosiran reported improvement in their overall health status, daily functioning, and QOL as compared to placebo

Abbreviations: AAR, annualized attack rate; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALAS1, 5-aminolevulinic acid synthase 1; ANCOVA, analysis of covariance; AUC, area under the curve; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; EQ-5D-5L VAS, 5-level EuroQol 5-Dimensions Questionnaire visual analog scale; GalNAc, *N*-acetylgalactosamine; HMBS, hydroxymethylbilane synthase; IV, intravenous; LS. Least squares; MMRM, Mixed-Effect Model Repeated Measure; NRS, Numeric Rating Scale; PBG, porphobilinogen; PCS, Physical Component Summary; PGIC, Patient Global Impression of Change; PPEQ, Porphyria Patient Experience Questionnaire; PRO, patient-reported outcome; Q, question; qM, every month; QOL, quality of life; Q-Q, quantile–quantile; RNAi, ribonucleic acid interference; SC, subcutaneous; SD, standard deviation; SF-12, Short-Form (12-item) Health Survey; ULN, upper limit of normal.

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QR Placeholder