ENVISION, a Phase 3 Study to Evaluate the Efficacy and Safety of Givosiran, an Investigational RNAi Therapeutic Targeting Aminolevulinic Acid Synthase 1, in Patients with Acute Hepatic Porphyria

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Introduction

Acute Hepatic Porphyria (AHP)

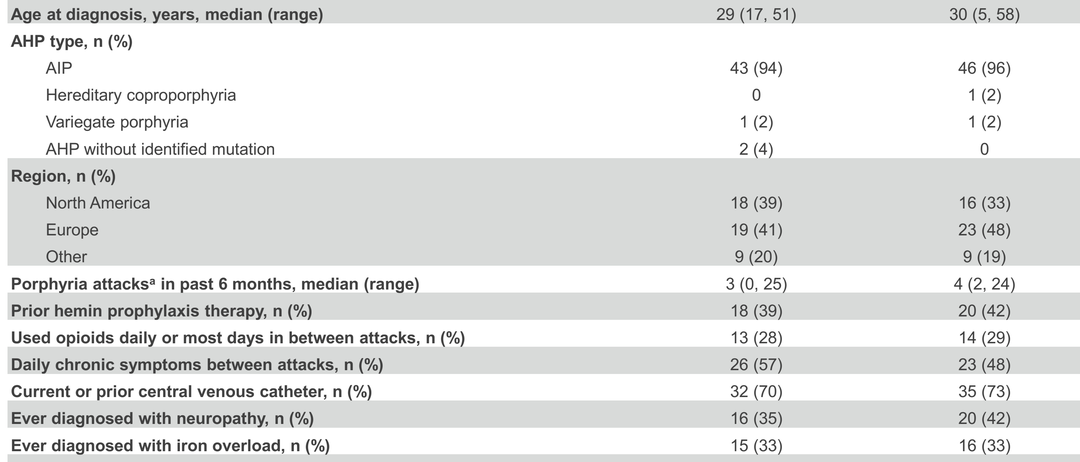
- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in liver[1,2]
- Induction of aminolevulinic acid synthase 1 (ALAS1) leads to accumulation of toxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), with ALA believed to be the primary toxic intermediate that causes disease manifestations[3,4]
- Patients can experience acute, potentially life-threatening neurovisceral attacks, chronic symptoms (including pain, fatigue, nausea, and anxiety), and long-term complications (such as hypertension, chronic kidney disease, and liver disease); disability and social isolation are also common[5–9]
- Acute intermittent porphyria (AIP) is the most common form of AHP, with mutation in the *hydroxymethylbilane synthase* (*HMBS*) gene[10,11]

Givosiran

- Givosiran, a subcutaneously administered investigational RNAi therapeutic in development for the treatment of AHP, targets liver ALAS1 mRNA to reduce liver ALAS1 protein and lower ALA/PBG production to prevent attacks and disease symptoms[12]

Methods

- ENVISION was a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of subcutaneous givosiran in patients with AHP (**Figure 1**)



*Endpoints evaluated in patients with genetically confirmed AIP, unless otherwise noted

Results

Trial Population (Table 1)

- Overall, 94 patients (from 36 sites in 18 countries) were enrolled and randomized to receive givosiran (n=48) or placebo (n=46)
- Comorbidities included liver disease, chronic kidney disease, neuropathy, and iron overload

Table 1. Baseline Demographics and Characteristics of Patients

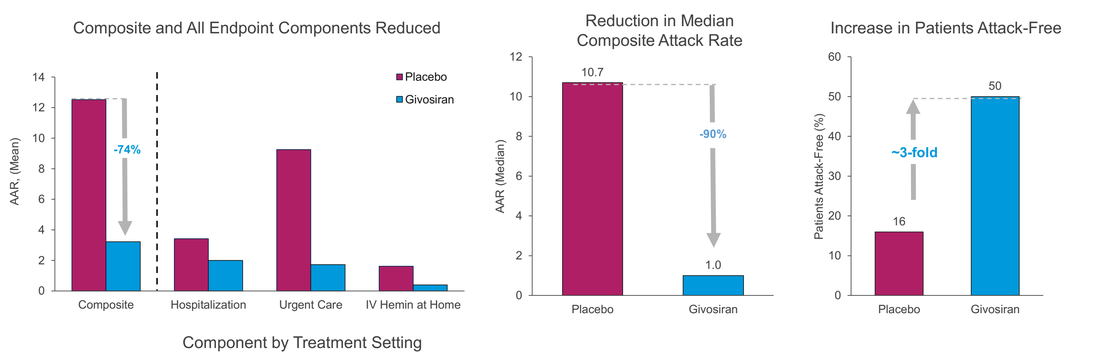
Characteristic	Placebo (n=46)	Givosiran (n=48)
Age, years, median (range)	36 (20, 60)	42 (19, 65)
Female, n (%)	41 (89)	43 (90)
Race, n (%)		
White/Caucasian	34 (74)	39 (81)
Asian	7 (15)	8 (17)
Other	5 (11)	1 (2)
Age at diagnosis, years, median (range)	29 (17, 51)	30 (5, 58)
AHP type, n (%)		
AIP	43 (94)	46 (96)
Hereditary coproporphyria	0	1 (2)
Variegate porphyria	1 (2)	1 (2)
AHP without identified mutation	2 (4)	0
Region, n (%)		
North America	18 (39)	16 (33)
Europe	19 (41)	23 (48)
Other	9 (20)	9 (19)
Porphyria attacks[a] in past 6 months, median (range)	3 (0, 25)	4 (2, 24)
Prior hemin prophylaxis therapy, n (%)	18 (39)	20 (42)
Used opioids daily or most days in between attacks, n (%)	13 (28)	14 (29)
Daily chronic symptoms between attacks, n (%)	26 (57)	23 (48)
Current or prior central venous catheter, n (%)	32 (70)	35 (73)
Ever diagnosed with neuropathy, n (%)	16 (35)	20 (42)
Ever diagnosed with iron overload, n (%)	15 (33)	16 (33)
Liver transaminase elevation >ULN[b], n (%)	3 (7)	13 (27)
eGFR <60 mL/min/1.73 m^2, n (%)	11 (24)	16 (33)

[a]Protocol qualifying attacks: ≥2 attacks in past 6 months requiring hospitalization, urgent healthcare visit, or IV hemin at home
[b]Worst study value of ALT or AST prior to dosing: >ULN and ≤3×ULN

Primary Efficacy Endpoint

- In patients with AIP, mean (standard deviation) composite annualized attack rate (AAR, attacks requiring hospitalization, urgent healthcare visit, or intravenous [IV] hemin at home) was 3.2 (2.25, 4.59) in the givosiran group, compared with 12.5 (9.35, 16.76), a 74% reduction ($p=6.04\times10^{-9}$; Figure 2)
- Treatment with givosiran was favored compared to placebo across all subgroups

Figure 2. Primary Efficacy Endpoint: AAR in Patients with AIP



Mean AAR was derived using the negative binomial regression model; mean AAR for components was duration-weighted AAR; median AAR was calculated from the individual's patient's AAR

Secondary Endpoints

- In patients with AIP, givosiran treatment also significantly improved mean ALA and PBG levels, hemin usage, and daily worst pain scores compared with placebo, and composite AAR in patients with AHP (**Table 2**)

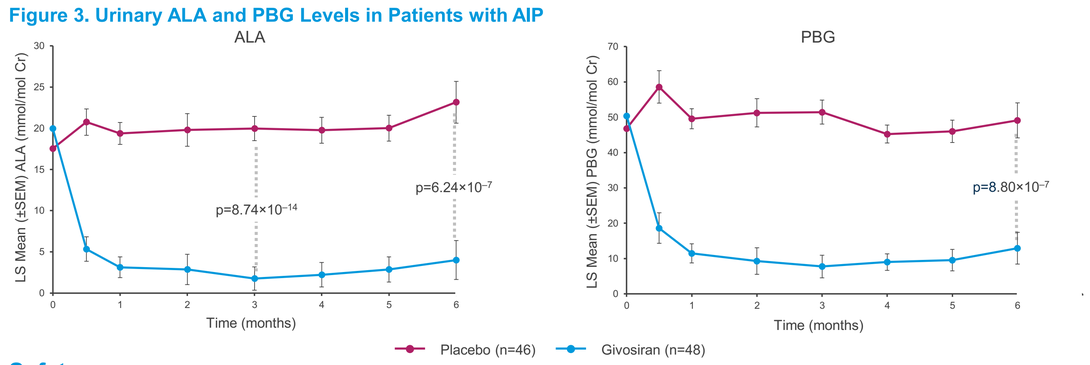
Table 2. Secondary Efficacy Endpoints

Secondary Endpoints[a]	Placebo (n=43/46[b])	Givosiran (n=46/48[b])	Treatment Difference (95% CI)	P-Value
LS mean ALA in AIP at Month 3, mmol/mol Cr[f]	19.96	1.75	–18 (–22.3, –14.2)	8.74×10^{-14}
LS mean ALA in AIP at Month 6, mmol/mol Cr[f]	23.15	4.01	–19 (–26.0, –12.2)	6.24×10^{-7}
LS mean PBG in AIP at Month 6, mmol/mol Cr[f]	49.11	12.9	–36 (–49.7, –22.7)	8.80×10^{-7}
Mean annualized days on hemin in AIP[f]	29.71	6.77	0.23 (0.11, 0.45)	2.36×10^{-5}
Mean composite attack rate in AHP[f]	12.26	3.35	0.27 (0.17, 0.43)	1.36×10^{-8}
Daily worst pain in AIP (AUC of change from baseline)[c]	–0.196	–12.876	–12.680 (–25.526, 0.166)	0.0530 (ANCOVA)[d] 0.0455 (Wilcoxon)
Daily worst fatigue in AIP (AUC of change from baseline)[c]	–4.208	–11.148	–6.940 (–19.837, 5.957)	0.2876
Daily worst nausea in AIP (AUC of change from baseline)[c]	–4.011	1.481	5.492 (–4.000, 14.984)	0.2532
PCS of SF-12 change from baseline in AIP[e]	1.431	5.369	3.939 (0.592, 7.285)	0.0216

[a]Treatment differences are based on estimated LS mean difference (givosiran – placebo) with the exception of annualized days on hemin and composite attack rate endpoints, for which annualized rates are estimated and the treatment differences are measured by risk ratio (givosiran/placebo)
[b]n=46 for placebo and n=48 for givosiran for composite attack rate in AHP endpoint
[c]A higher score indicates worse manifestation
[d]Pain data not normally distributed; ANCOVA method not valid. Post hoc analysis using non-parametric stratified Wilcoxon method
[e]A higher score indicates better physical health and functioning
[f]Statistical significance in pre-specified hierarchical testing met

- Givosiran showed rapid, robust, and sustained reductions in urinary ALA and PBG over six months
- In patients with AIP, mean ALA and PBG were reduced by 77% and 76%, respectively, compared with baseline at 6 months
- Median urinary ALA and PBG were reduced by 86% and 91%, respectively, compared with baseline at 6 months (**Figure 3**)

Figure 3. Urinary ALA and PBG Levels in Patients with AIP



Safety

- Adverse events (AEs) occurred in 90% of patients in the givosiran group and 80% of patients in the placebo group (**Table 3**)
- All patients completed the 6-month double-blind period with 1 patient discontinuing givosiran for an ALT elevation meeting protocol stopping rules (>8×upper limit of normal [ULN])

Table 3. Safety

Adverse Event, n of patients (%)	Placebo (n=46)	Givosiran (n=48)
At least 1 AE	37 (80)	43 (90)
At least 1 serious AE	4 (9)	10 (21)
At least 1 severe AE	5 (11)	8 (17)
At least 1 AE leading to treatment discontinuation	0	1 (2)
Deaths	0	0
Serious AEs		
Chronic kidney disease	0	2 (4)
Asthma	0	1 (2)
Device-related infection	2 (4)	1 (2)
Gastroenteritis	0	1 (2)
Hypoglycemia	0	1 (2)
Liver function test abnormal	0	1 (2)
Major depression	0	1 (2)
Pain management	0	1 (2)
Pyrexia	1 (2)	1 (2)
Escherichia urinary tract infection	1 (2)	0
Fractured sacrum	1 (2)	0
Sepsis	1 (2)	0
Septic shock	1 (2)	0

- Two serious AEs in givosiran-treated patients reported as study drug related (abnormal liver function test and chronic kidney disease); no serious AEs in placebo-treated patients reported as study drug related
- Two chronic kidney disease AEs considered serious due to elective hospitalization for diagnostic evaluation; renal biopsies consistent with underlying disease. No signs of immune complex or primary glomerular renal disorders
- ALT >3×ULN in 7 (15%) givosiran-treated patients and 1 (2%) placebo-treated patient
  - 1 givosiran patient discontinued (mentioned previously); 1 givosiran patient had dose interrupted due to a protocol-specified rule, with resumption at 1.25 mg/kg; 5 other givosiran-treated patients had resolution with ongoing dosing
- ALT elevations were mild to moderate, occurred ~3–5 months after givosiran started, and resolved or stabilized by Month 6
- 7 (15%) givosiran patients and 2 (4%) placebo patients had renal AEs of increased creatinine and/or decreased estimated glomerular filtration rate (eGFR)
  - Most were mild to moderate in severity and resolved without treatment interruption
- Generally small increases in serum creatinine (median change 0.07 mg/dL at Month 3) and decreases in eGFR with givosiran that resolved or stabilized by Month 6

Open-Label Extension (OLE) Period

- Maintenance of reduction of composite porphyria attack rate and urinary ALA levels in AHP patients who continued with givosiran treatment, along with rapid and sustained lowering of composite porphyria attack rate and urinary ALA levels in placebo AHP patients who crossed over to givosiran in the OLE period (data as of May 31 2019)
- Safety profile consistent with that observed in the double-blind period

Conclusions

- Givosiran resulted in a 74% mean reduction in annualized composite rate of porphyria attacks relative to placebo in patients with AIP
  - Corresponding 90% reduction in median AAR, with 50% of patients on givosiran attack-free (16.3% for placebo)
  - All components of composite attacks reduced and all subgroup analyses favored givosiran
  - 73% reduction in mean AAR in patients with any AHP relative to placebo
- Givosiran resulted in a mean reduction in days of hemin use of 77% compared to placebo
- Givosiran led to sustained lowering from baseline of ALA (86%) and PBG (91%), the toxic heme intermediates causal for attacks and other AHP disease manifestations
- Overall safety and tolerability profile is acceptable in AHP, a serious illness
  - Majority of ALT elevations were mild to moderate, occurred ~3–5 months after givosiran started, and resolved or stabilized by Month 6
  - 7 (15%) givosiran patients and 2 (4.3%) placebo patients had renal AEs of increased creatinine and/or decreased eGFR, including 5 AEs of CKD in givosiran patients
  - Generally small increases in serum creatinine (median change 0.07 mg/dL at Month 3) and decreases in eGFR with givosiran that resolved or stabilized by Month 6
- OLE data to-date support maintenance of reduction in composite AAR and urinary ALA levels, with a consistent safety profile

Abbreviations: AAR, annualized attack rate; AE, adverse event; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALAS1, ALA synthase 1; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST, aspartate transaminase; AUC, area under the curve; CI, confidence interval; Cr, creatinine; eGFR, estimated glomerular filtration rate; HMBS, hydroxymethylbilane synthase; IV, intravenous; LS, least squares; OLE, open-label extension; PBG, porphobilinogen; PCS, Physical Component Summary; qM, every month; RNAi, ribonucleic acid interference; SC, subcutaneous; SEM, standard error of the mean; SF-12, Short-Form (12-item) Health Survey; ULN, upper limit of normal.

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