Clinical Outcomes in Patients with Acute Hepatic Porphyria Treated with Givosiran Who Stopped Hemin Prophylaxis at Study Entry: A Post-hoc Analysis of Data from the Phase 3 ENVISION Study Through Month 12

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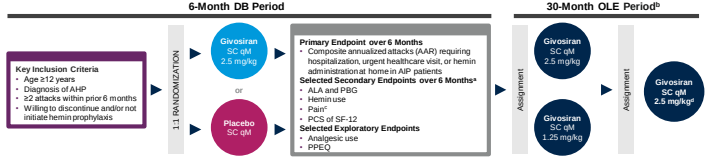
Introduction

- AHP is a family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in the liver[1,2]
- Induction of ALAS1 leads to accumulation of toxic heme intermediates ALA and PBG resulting in neurovisceral attacks, which commonly manifest as severe abdominal pain and can be life-threatening.[3,4]
- Some patients also experience debilitating chronic symptoms including diffuse abdominal pain, fatigue, nausea, and anxiety[3–5]; other long-term complications and comorbidities include hypertension, chronic kidney disease, and liver disease.[3,6–9]
- Current options for managing attacks include the removal of triggering factors and treatment with intravenous (IV) opioids, glucose, and hemin.[4,10]
- Hemin is approved to treat acute attacks; however, it is sometimes used off-label prophylactically.[11]
  - Chronic hemin use often requires an indwelling central venous catheter, and can lead to iron overload.[4,12]
- In the ENVISION study, givosiran, an RNAi therapeutic, reduced the composite porphyria annualized attack rate (AAR) compared to placebo in patients with AHP[13], was recently approved in the USA for the treatment of AHP in adults and in the EU for the treatment of AHP in adults and adolescents aged 12 years or older.[4,14,15]
- A post-hoc analysis was conducted to evaluate outcomes in AHP patients with or without prior hemin prophylaxis prior to screening; patients in ENVISION had to discontinue hemin prophylaxis but could receive hemin for attacks during the study.

Methods

- 94 patients with AHP enrolled in ENVISION (**Figure 1**); all completed the 6-month double-blind (DB) period, and 93 eligible patients entered the 30-month open-label extension (OLE) period.
  - Patients were required to discontinue prophylactic hemin treatment at study entry, but could receive hemin for acute attacks
- All analyses in this post-hoc analysis are descriptive.

Figure 1. ENVISION Phase 3 Study Design



[a]Endpoints evaluated in patients with genetically confirmed AIP, unless otherwise noted, at 6 months. [b]All endpoints listed above were considered exploratory in OLE period. [c]Severity of daily pain was measured via question #3 from the Brief Pain Inventory-Short-Form Numeric Rating Scale (NRS), where patients chose a rating from 0 (no pain) to 10 (pain as bad as you can imagine) to describe the worst level of pain experienced over the past 24 hours. [d]Patients initially received 2.5 mg/kg or 1.25 mg/kg. Amendment 5 increased the dose of all patients to 2.5 mg/kg monthly.

Results

Baseline Demographics and Disease Characteristics

- Overall, 38/94 patients (40%) had received prior hemin prophylaxis before study entry.
  - Approximately 40% of these patients were receiving a weekly hemin regimen
- Baseline demographics and characteristics were generally similar between the subgroups with or without prior hemin prophylaxis (**Table 1**).
  - Patients with prior hemin prophylaxis had more frequent central venous catheter use (87% vs 61%) and central venous access complications (39% vs 29%) than those without hemin prophylaxis
  - Patients with prior hemin prophylaxis more frequently had iron overload (55% vs 18%)

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Prior Hemin Prophylaxis		No Prior Hemin Prophylaxis	
	Placebo (N=18)	Givosiran (N=20)	Placebo (N=28)	Givosiran (N=28)
Age at diagnosis, years, median (range)	29.6 (16.9–44.1)	32.4 (16.2–47.7)	28.0 (18.0–51.4)	28.1 (5.0–58.1)
Years since diagnosis, median (range)	7.1 (0.7–38.5)	6.6 (0.2–35.3)	3.7 (0.1–25.0)	7.2 (0.4–43.3)
Historical AAR[a], median (range)	9.0 (4–38)	9.0 (4–32)	6.0 (0–46)	8.0 (4–34)
Chronic symptoms daily or most days between attacks, n (%)	9 (50)	7 (35)	17 (61)	16 (57)
Opioid use daily or most days between attacks, n (%)	6 (33)	8 (40)	7 (25)	6 (21)
Current or prior catheter use, n (%)	16 (89)	17 (85)	16 (57)	18 (64)
Complications related to central venous access, n (%)	8 (44)	7 (35)	8 (29)	8 (29)
Thrombosis	1 (6)	2 (10)	1 (4)	3 (11)
Infection	4 (22)	3 (15)	5 (18)	5 (18)
Catheter occlusion/malfunction	3 (17)	6 (30)	6 (21)	6 (21)
Other	1 (6)	1 (5)	2 (7)	0
Diagnosed iron overload, n (%)	11 (61)	10 (50)	4 (14)	6 (21)
Treated	7 (39)	6 (30)	1 (4)	3 (11)
Iron chelation therapy	1 (6)	1 (5)	0	2 (7)
Phlebotomy	6 (33)	5 (25)	1 (4)	1 (4)
Other	0	2 (10)	0	0

[a]Based on the number of attacks requiring hospitalization, healthcare facility visit, or hemin use at home during the 6 months prior to randomization

Results Continued

AAR[a]

- Patients with prior hemin prophylaxis (median historical AAR: 9.0), had a >90% reduction in median AAR with givosiran vs placebo in the DB period (**Figure 2**).
  - A similar reduction in median AAR (100%) observed with givosiran vs placebo in those without prior hemin prophylaxis (median historical AAR: 7.0)
- Median AAR reductions were maintained or enhanced during the OLE period.
- In the DB period, the percentage of patients with zero composite attacks was higher with givosiran treatment vs placebo, regardless of prior hemin prophylaxis (**Figure 3**).
  - 45.0% vs 5.6% (hemin prophylaxis); 51.9% vs 25.0% (no hemin prophylaxis)
- Further increases in the percentage of patients with zero attacks were observed among patients who continued givosiran treatment or crossed over from placebo to givosiran in the OLE (**Figure 3**).

Figure 2. Median AAR

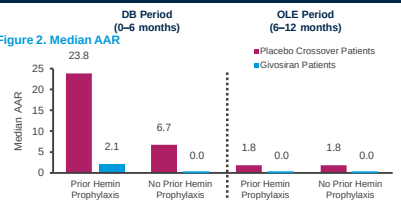
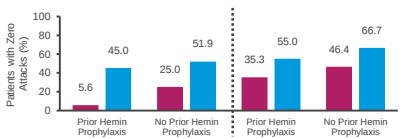


Figure 3. Patients with Zero Attacks

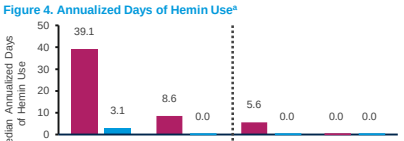


Hemin Use (for treatment of acute attacks)

- Median annualized days of hemin use was lower with givosiran vs placebo in the DB period, regardless of prior hemin prophylaxis.
  - During the OLE, median annualized days of hemin use in placebo crossover patients decreased to 5.6 (with prior hemin prophylaxis) and to 0 (without prior hemin prophylaxis) (**Figure 4**).

[a]Defined as attacks requiring hospitalization, urgent care, or IV hemin at home

Figure 4. Annualized Days of Hemin Use[a]



[a]Hemin prophylaxis was not allowed during the study; days of hemin use therefore refers only to hemin used to treat attacks

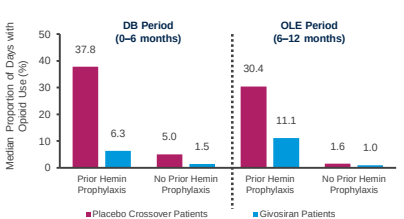
Table 2. Daily Worst Pain

Characteristic	Prior Hemin Prophylaxis		No Prior Hemin Prophylaxis	
	Placebo Crossover Patients (N=18)	Givosiran Patients (N=20)	Placebo Crossover Patients (N=28)	Givosiran Patients (N=28)
Baseline Pain Score (NRS), median	3.9	2.2	3.4	2.9
Median Change from Baseline, DB period (0–6 mo)	0.2	-0.5	-0.02	-0.2
Median Change from Baseline, OLE period (6–12 mo)	-0.4	-1.1	-0.9	-0.4

Pain

- Patients had reduced pain when treated with givosiran in 6-month DB period, regardless of prior hemin prophylaxis use, compared to an increase/no decrease observed in the placebo group **(Table 2).**
- Similar reductions in pain were seen in placebo crossover patients as in patients on givosiran in DB period, and a continued reduction in givosiran patients regardless of prior hemin prophylaxis (**Table 2**).
- Patients receiving givosiran during the 6-month DB period had fewer days of opioid use than those receiving placebo regardless of prior hemin prophylaxis status **(Figure 5).**
- This difference was seen in placebo crossover patients both the prior hemin prophylaxis and no prior hemin prophylaxis subgroups in the OLE period (**Figure 5**).

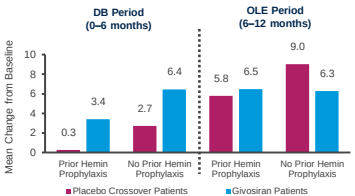
Figure 5. Proportion of Days with Opioid Use



QOL and Patient Perspective

- Givosiran-treated patients had greater mean changes from baseline in SF-12 PCS[a] at Month 6 of DB period than placebo-treated patients, regardless of prior hemin prophylaxis (**Figure 6**).
  - Data from other chronic diseases suggest that the improvements seen in givosiran patients represent clinically meaningful differences (≥2–5 point increases)[16,17]
- Continued givosiran treatment resulted in further improvement in SF-12 PCS at Month 12 in patients with prior hemin prophylaxis.
- Placebo crossover patients showed an increase at Month 12 compared with Month 6 regardless of prior hemin prophylaxis.

Figure 6. SF-12 PCS Mean Change from Baseline

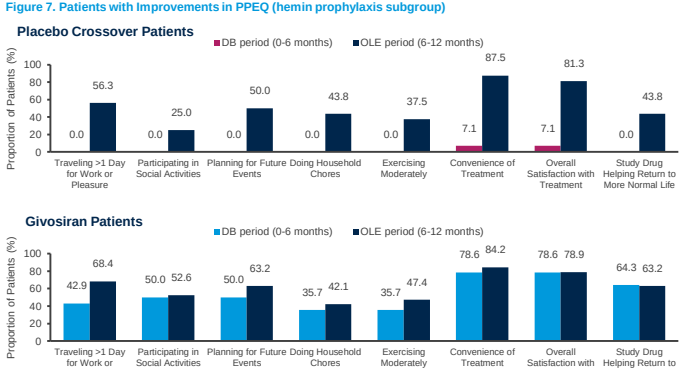


[a]PCS of the Short-Form (12-item) Health Survey, a 12-question measure capturing global QOL and overall health status over the past 4 weeks

- Among patients with prior hemin prophylaxis, there was improvement (higher proportion of much better or always) in all PPEQ[a] categories at Month 6 for givosiran vs placebo (**Figure 7**).
  - Placebo crossover patients showed improvement in all PPEQ categories during the OLE

[a]A custom instrument containing eight questions to assess treatment experience, activities of daily living, and functional status on a 5-point global rating of change scale

Figure 7. Patients with Improvements in PPEQ (hemin prophylaxis subgroup)



Summary

- Regardless of prior hemin prophylaxis patients in the ENVISION study showed:
  - Clinically meaningful reductions in porphyria attacks with givosiran treatment versus placebo
    - Reductions in AAR were observed in those who continued to receive givosiran during the OLE period
    - A similar benefit in AAR was observed in placebo crossover patients who received givosiran during the OLE period
    - 55% and 67% of patients who continued on givosiran had zero attacks in the OLE period with and without prior hemin prophylaxis use, respectively
  - Reductions in hemin use (for treatment of acute attacks) and in pain and use of opioids with givosiran treatment vs placebo
  - Greater improvements in overall QOL with givosiran treatment vs placebo, including improvements in physical health and ability to do activities of daily living
- Overall, patients who received hemin prophylaxis prior to ENVISION showed substantial clinical benefit when treated with givosiran, similar to those without prior hemin prophylaxis.

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Abbreviations: AAR, annualized attack rate of composite porphyria attacks; AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; DB, double-blind; IV, intravenous; NRS, numerical rating scale for assessing pain intensity; OLE, open-label extension; PBG, porphobilinogen; PCS, Physical Component Summary; PPEQ, Porphyria Patient Experience Questionnaire; qM, every month; RNAi, RNA interference; SC, subcutaneous; SEM, standard error of the mean; SF-12, Short-Form (12-Item) Health Survey. **References:** 1. Puy et al. *Am J Hum Genet* 1997;60:1373–83; 2. Balwani & Desnick. *Blood* 2012;120:4496–504; 3. Gouya et al. *Hepatology* 2019; DOI:10.1002/hep.30936; 4. Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; 5. Simon et al. *Patient* 2018;11:527–37; 6. Bonkovsky et al. *Am J Med* 2014;127:1233–41; 7. Stewart. *J Clin Pathol* 2012;65:976–80; 8. Pallet et al. *Kidney Int* 2015;88:386–95; 9. Andersson et al. *J Intern Med* 1996;240:195–201; 10. Stein et al. *Br J Haematol* 2017;176:527–38; 11. Balwani et al. *Hepatology* 2017;66:1314–22; 12. Wang et al. *Hepatol Commun* 2018;2:193–206; 13. Balwani et al. *N Engl J Med* 2020;382:2289–301; 14. GIVLAARI Highlights of Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212194s000lbl.pdf. Accessed October 7, 2020; 15. GIVLAARI EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf. Accessed October 7, 2020; 16. Clement et al. *Knee Surg Sports Traumatol Arthrosc* 2014;22:1933–9; 17. Parker et al. *J Neurosurg Spine* 2012;16:471–8