Hemin Use in Patients with Acute Hepatic Porphyria Treated with Givosiran: A Post Hoc Analysis of the Phase 3 ENVISION Study

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Introduction

Acute Hepatic Porphyria (AHP)

- Family of rare, genetic diseases due to a deficiency in one of the enzymes in hepatic heme biosynthesis[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 disease 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[6–8]
- Comorbidities include hypertension, CKD, and liver disease[3,6,9–11]

Treatment Landscape

- Hemin used to treat acute attacks and sometimes prophylactically off-label treatment to prevent attacks[7]
  - Prophylactic use often requires an indwelling central venous catheter and patients can experience iron overload (hemin is 9% iron by weight)[12–14]
- Current options for managing attacks include the removal of triggering factors and treatment with intravenous (IV) opioids, glucose, and hemin
- Unmet need for therapies to prevent attacks and chronic disease manifestations

Givosiran

- Subcutaneously administered RNAi therapeutic that specifically targets ALAS1 messenger RNA in liver to reduce disease-causing neurotoxic intermediates ALA and PBG[15,16,17]
- Approved for treatment of AHP in adults in the US and adults and adolescents aged 12 years and older in the EU[17,18] following results of the Phase 3 ENVISION trial
  - During the 6-month double-blind period of ENVISION, treatment with givosiran resulted in a 74% reduction in mean composite AAR compared with placebo ($p<0.0001$) in patients with AIP[17]
  - Givosiran has an acceptable safety profile; givosiran is contraindicated in patients with severe hypersensitivity to givosiran and has warnings and precautions for anaphylactic reaction, hepatic toxicity, and renal toxicity[18,19]

Objective

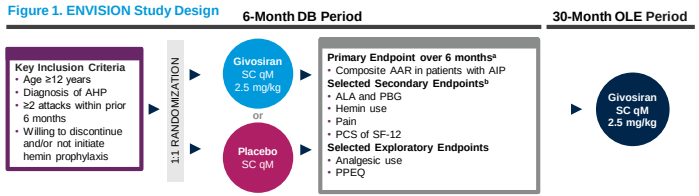
- A post hoc analysis was performed to evaluate hemin use (for the treatment of acute attacks) by subgroups during the 6-month ENVISION trial

Methods

ENVISION Phase 3 Study

- ENVISION (NCT03338816) was a global, multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial with an open-label extension to evaluate the efficacy and safety of subcutaneous givosiran in patients with AHP experiencing frequent attacks (**Figure 1**)

Figure 1. ENVISION 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
AAR, annualized attack rate; AHP, acute hepatic porphyria; ALA, 5-aminolevulinic acid; PBG, porphobilinogen; PCS, Physical Component Summary; PPEQ, Porphyria Patient Experience Questionnaire; qM, every month; SC, subcutaneous; SF-12, Short-Form (12-item) Health Survey

- Eligible patients were aged ≥12 years with an AHP diagnosis and ≥2 composite porphyria attacks within prior 6 months or were receiving hemin prophylaxis. Patients were required to stop prophylactic hemin use prior to screening but were able to receive hemin if experiencing an attack during the study
- Baseline disease characteristics included proportion of patients with history of hemin prophylaxis, medical history of iron overload, or complications related to chronic indwelling venous catheters or other central venous access
- Annualized days of hemin use in patients with AHP during the 6-month, double-blind period were analyzed by history of chronic symptoms, history of opioid use between attacks, and historical AAR at baseline

Results

Baseline Demographics

- ENVISION enrolled 94 patients with AHP at 36 sites in 18 countries (**Table 1**)
- Overall, 89% of patients were female, with a median of 8 attacks in the preceding year, and 29% of patients used opioids daily/most days between attacks at baseline
- 40% were on hemin prophylaxis prior to study
  - 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 (as reported via medical history) than those without hemin prophylaxis (55% vs 18%, respectively)

Table 1. Baseline Demographics and Characteristics

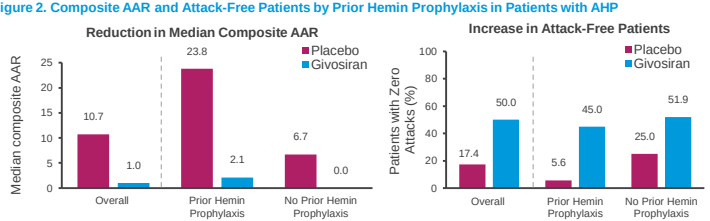
Characteristic[a]	Prior Hemin Prophylaxis (n=38)	No Prior Hemin Prophylaxis (n=56)	All Patients (n=94)
Mean (SD) age at diagnosis, years	31.1 (9.0)	29.5 (11.2)	30.1 (10.3)
Mean (SD) time since diagnosis, years	10.3 (9.5)	9.3 (10.4)	9.7 (10.0)
Median (range) historical AAR[b]	9 (4–38)	7 (0–46)	8 (0–46)
Prior chronic symptoms[c], n (%)	16 (42)	33 (57)	49 (52)
Prior chronic opioid use[d], n (%)	14 (37)	13 (23)	27 (29)
Prior hemin prophylaxis[e], n (%)	38 (100)	0 (0)	38 (40)
Diagnosed with iron overload, n (%)	21 (55)	10 (18)	31 (33)
Treated	13 (34)	4 (7)	17 (18)
Iron chelation therapy	2 (5)	2 (4)	4 (4)
Phlebotomy	11 (29)	2 (4)	13 (14)
Other	2 (5)	0 (0)	2 (2)
Chronic indwelling venous catheters, n (%)	33 (87)	34 (61)	67 (71)
Complications related to central venous access, n (%)	15 (39)	16 (29)	31 (33)
Thrombosis	3 (8)	4(7)	7 (10)
Infection	7(18)	10 (18)	17 (18)
Catheter occlusion/malfunction	9 (24)	12 (21)	21 (22)
Other	2 (5)	2 (4)	4 (4)
Any Complication	15 (40)	16 (29)	31 (33)
Diagnosed with neuropathy, n (%)			
Yes	12 (32)	24 (43)	36 (30)
No	26 (68)	32 (57)	58 (62)

[a]All values are n (%) unless otherwise stated; [b]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home; [c]Patients experienced symptoms of porphyria when not having an attack daily or on most days prior to the study; [d]Patients taking opioids for porphyria when not having an attack daily or on most days; [e]Supplemental medical history

Porphyria Composite Annualized Attack Rate (AAR)

- Givosiran resulted in a 90% reduction in median composite AAR in patients with AHP relative to placebo and an ~3-fold increase in the percentage of attack-free patients during the 6-month double-blind period **(Figure 2)**
  - All subgroup analyses, including prior hemin prophylaxis **(Figure 2),** showed givosiran treatment benefit in reduction in attack rates and higher proportion of patients with 0 attacks

Figure 2. Composite AAR and Attack-Free Patients by Prior Hemin Prophylaxis in Patients with AHP

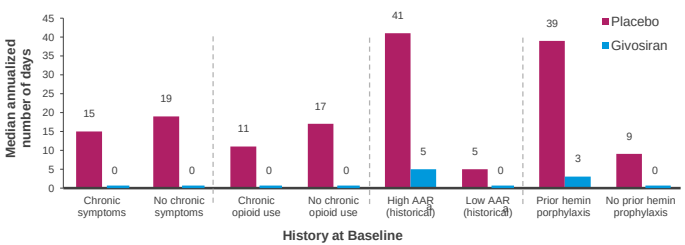


Median AAR was calculated from individual patient's AAR

Hemin Use (for the Treatment of Acute Attacks)

- Patients with AHP receiving givosiran experienced a 74% (nominal $p=0.0002$) reduction in annualized days of hemin use compared with placebo during the 6-month double-blind period
- Overall, 54% of givosiran-treated patients had 0 days of hemin use compared with 26% of placebo patients
- Givosiran-treated patients had fewer median annualized days of hemin use compared with those on placebo, whether or not at baseline they had a history of chronic symptoms, a history of opioid use between attacks, or a high or low historical AAR (**Figure 3**)
- The median annualized days of hemin use was 0 for givosiran-treated patients in all subgroups except for patients with high historical AAR (5 days vs 41 days for placebo patients)
- Median ferritin levels were reduced by 7% from baseline in givosiran-treated patients at 6 months compared with a 3% increase in placebo patients, potentially reflecting reduced hemin usage

Figure 3. Median Annualized Days of Hemin Use (for the Treatment of Acute Attacks) in Patients with AHP



[a]High and low historical AARs were based on numbers of attacks during the 6 months preceding the study period. For patients on hemin prophylaxis: low <7, high ≥7; those not on hemin prophylaxis: low <12, high ≥12

Conclusions

- Patients with a history of prophylactic hemin use were more likely to have central venous catheters, related complications, or iron overload than those without a history of hemin prophylaxis
- Regardless of prior hemin prophylaxis, treatment with givosiran resulted in a reduction in attack rates and a higher proportion of patients who were attack free compared with placebo treatment
- Along with a significant reduction in composite porphyria attacks, givosiran treatment led to a clinically meaningful reduction in annualized hemin use (for treatment of acute attacks) in patients with AHP experiencing frequent attacks
  - This was regardless of whether patients had a history of chronic symptoms, history of opioid use, or a high or low rate of historical attacks at study entry
- Reducing hemin use may decrease complications associated with hemin treatment, which typically requires IV administration in a hospital setting, and is associated with acute (e.g., headache, fever, phlebitis) and chronic (e.g., iron overload, venous obliteration, indwelling central venous catheter complications) side effects[12,14,19]

Acknowledgments: We thank ENVISION investigators, study site staff, patient organizations, and participating patients. Editorial assistance provided by Stephen Whiting (PhD) of Adelphi Communications Ltd, Macclesfield, UK, was funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice (GPP3) guidelines. **Funding:** This study was sponsored by Alnylam Pharmaceuticals.

Abbreviations: AAR, annualized attack rate; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinic acid; ALAS1, 5-aminolevulinic acid synthase 1; CI, confidence interval; IV, intravenous; PBG, porphobilinogen; PCS, Physical Component Summary; qM, every month; RNAi, ribonucleic acid interference; SC, subcutaneous; SF-12, Short-Form (12-item) Health Survey; SD, standard deviation.

References: 1. Puy et al. *Am J Hum Genet* 1997;60:1373–83; 2. Balwani & Desnick. *Blood* 2012;120:4496–504; 3. Bonkovsky et al. *Am J Med* 2014;127:1233–41; 4. Elder et al. *JIMD* 2013;36:849–57; 5. Bissell et al. Am J Med 2015;128:313–7; 6. Gouya et al. *Hepatology* 2020 71:1546–1558; 7. Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; 8. Simon et al. *Patient* 2018;11:527–37; 9. Stewart. *J Clin Pathol* 2012;65:976–80; 10. Pallet et al. *Kidney Int* 2015;88:386–95; 11. Andersson et al. *J Intern Med* 1996;240:195–201; 12. Normosang 25 mg/ml, concentrate for solution for infusion. Summary of product characteristics. 2019. Available from: https://www.medicines.org.uk/emc/product/6235/smpc; 13. Stein et al. *Br J Haematol* 2017;176:527–38; 14. Marsden et al. *JIMD Rep* 2015;22:57–65; 15. Sardh et al. N Engl J Med 2019;380:549–58; 16. Chan et al. Mol Ther Nucleic Acids 2014;4:e263; 17. Balwani et al. N Engl J Med 2020; 382:2289-301. 18. GIVLAARI US Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0212194s000lbl.pdf (accessed September 21, 2020); 19. GIVLAARI EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (accessed September 21, 2020); 20. Wang et al. *Hepatol Commun* 2018; 3: 193-206