Characteristics of Patients Treated with Givosiran in ELEVATE, a Global Observational Longitudinal Registry of Patients with Acute Hepatic Porphyria

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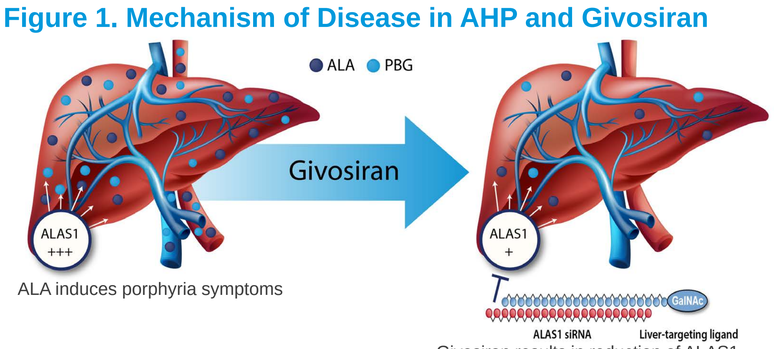
Conclusions

- **The ELEVATE registry is a real-world study designed to further elucidate the long-term effectiveness and safety of givosiran for the treatment of AHP and advance understanding of the natural history of AHP**
- **Givosiran-treated patients enrolled in ELEVATE were predominantly female (84%) and had a broad range of ages at entry (14-71 years) and symptom onset (6-63 years)**
  - **Overall, 90% had AIP and 25% had ever received-hemin prophylaxis**
  - **Pain, nausea, fatigue, tingling, numbness, weakness or paralysis, and anxiety were the most frequently reported AHP symptoms**
  - **Anxiety, other disease(s) independent of AHP, and hypertension were the 3 most common comorbidities**
- **Mean SF-12 summary scores were 43.6 points (mental health) and 42.8 points (physical health; range for both 0–100; higher score indicates better functioning[1])**
- **Prospective data collection is ongoing and will further characterize the disease burden over time and the long-term effectiveness and safety of givosiran for AHP treatment**
- **The ELEVATE registry will help increase our understanding of patient characteristics, diagnosis, and AHP chronicity**

Introduction

- Acute hepatic porphyria (AHP)
  - Group of rare, genetic disorders affecting multiple organ systems[2-4]
  - Characterized by acute attacks, chronic manifestations, and long-term complications, necessitating proactive management[2,3]
  - Caused by defects in hepatic heme biosynthesis leading to accumulation of neurotoxic heme intermediates delta-aminolevulinic acid (ALA) and porphobilinogen (PBG)[5,6]
- Patients with AHP can experience [2-4,7]
  - Potentially life-threatening acute attacks with symptoms including severe abdominal pain, nausea, vomiting, tachycardia, hypertension, hyponatremia, mental status changes, and muscle weakness
  - Chronic manifestations (eg, pain, fatigue, nausea between attacks), which impact daily functioning and quality of life (QOL)
- Givosiran is a subcutaneously administered RNA interference therapeutic approved for the treatment of AHP in adults in the US and adults and adolescents age ≥12 years in the EU that specifically targets hepatic ALAS1 mRNA in the liver to reduce ALA and PBG (**Figure 1**)

Figure 1. Mechanism of Disease in AHP and Givosiran

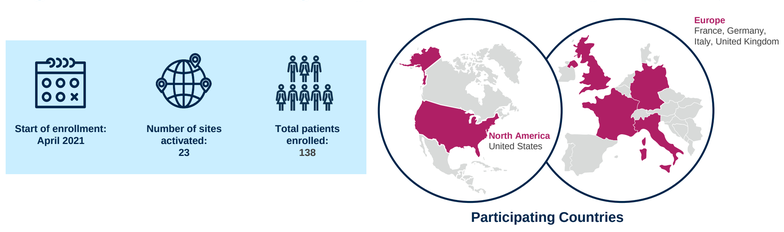


ALA induces porphyria symptoms

Givosiran results in reduction of ALAS1 activity and lowers ALA/PBG production to prevent attacks and disease symptoms

- In ENVISION (NCT03338816), long-term treatment over 36 months with givosiran was generally well tolerated and provided sustained benefit to patients with AHP[8,9]; findings included:
  - Reduced frequency of porphyria attacks and reduced hemin use
  - Improved patient-reported assessments of physical functioning and QOL
  - Injection-site reactions, nausea, and fatigue were the most common treatment-related AEs
- The ELEVATE registry (NCT04883905) is a global, prospective, observational study designed to characterize real-world long-term safety and effectiveness of givosiran and to describe the natural history and management of patients with AHP (**Figure 2**)

Figure 2. ELEVATE Registry Status (as of May 19, 2023)



- Here we report characteristics at ELEVATE enrollment of 93 patients with AHP who ever received treatment with givosiran (as of May 19, 2023)

Methods

- Registry patients have a documented AHP diagnosis, per physician's determination and are managed as per standard of care
- All patients provide written informed consent per local regulations or ethics committee requirements for inclusion of their health data in the registry
- No study-related procedures are recommended; medication is not provided
- Data are collected at least once every 12 months via routine clinical encounters for AHP, patient-reported outcome questionnaire (SF-12), or medical records
- The data collection window for these analyses is 12 months prior to registry enrollment to 3 months after registry enrollment, irrespective of timing of givosiran therapy
- Reported symptoms and status are not necessarily limited to a single time period with respect to givosiran (ie, prior to, during, or after treatment)
- For patients who were exposed to givosiran at enrollment, additional retrospective data are collected from the medical record to characterize clinical variables most proximal prior to givosiran initiation (within 12 months)

Results

- ELEVATE has enrolled 93 patients with AHP (84% female, median ages at symptom onset, 29 [range 6-63] years and at entry, 42 [range 14-71] years) from Europe and North America who ever received givosiran treatment (**Table 1**)
- AHP subtypes of enrolled patients include acute intermittent porphyria (AIP; N=84, 90.3%), variegate porphyria (VP; N=7, 7.5%) and hereditary coproporphyria (HCP; N=2, 2.2%); 32% had ever received medication for AHP other than givosiran; 25% had ever received hemin prophylaxis

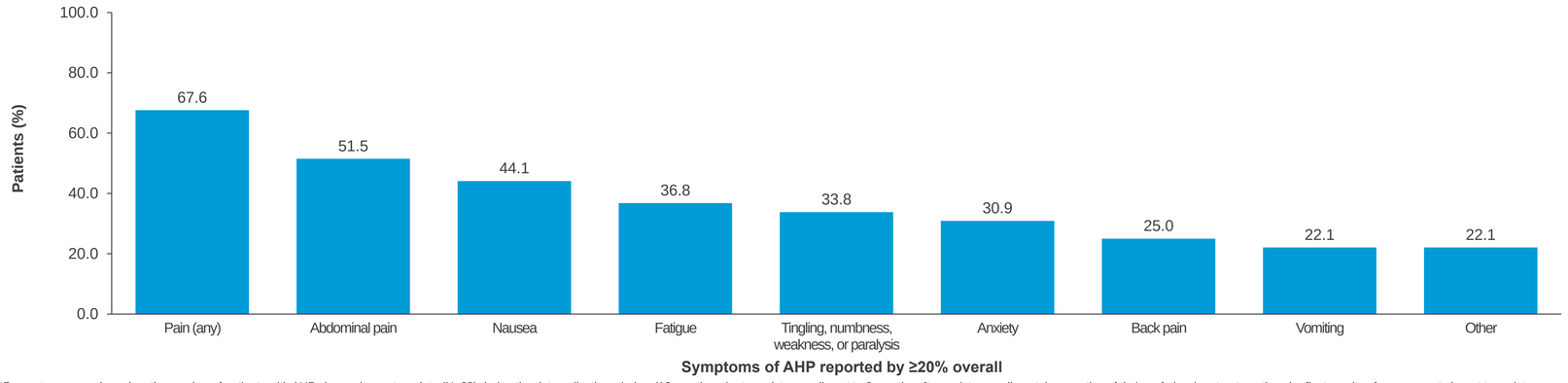
Table 1. ELEVATE Registry: Patient Characteristics at Enrollment

	Patients[a] Ever Treated with Givosiran			
	Total (N=93)	AIP (N=84, 90.3%)	VP (N=7, 7.5%)	HCP (N=2, 2.2%)
Age at entry, median (range), years	42 (14-71)	41.5 (14-71)	43 (34-62)	54.5 (43-66)
Age at symptom onset, median (range), years	29 (6-63)	29 (6-63)	39 (21-57)	19.5 (13-26)
Female, N (%)	78 (83.9)	69 (82.1)	7 (100.0)	2 (100.0)
Race, N (%)				
White	69 (74.2)	60 (71.4)	7 (100.0)	2 (100.0)
Black or African American	3 (3.2)	3 (3.6)	0 (0)	0 (0)
Asian	3 (3.2)	3 (3.6)	0 (0)	0 (0)
Unknown/not reported or collected[b]	18 (19.4)	18 (21.4)	0 (0)	0 (0)
Region, N (%)				
Europe	47 (50.5)	46 (54.8)	1 (14.3)	0 (0)
North America	46 (49.5)	38 (45.2)	6 (85.7)	2 (100.0)
Diagnostic test(s) for AHP[c], N (%)				
Genetic testing	64 (68.8)	59 (70.2)	4 (57.1)	1 (50.0)
PBG test	62 (66.7)	55 (65.5)	6 (85.7)	1 (50.0)
ALA test	49 (52.7)	45 (53.6)	3 (42.9)	1 (50.0)
Other biochemical testing	27 (29.0)	22 (26.2)	4 (57.1)	1 (50.0)
Fecal porphyrins	18 (19.4)	14 (16.7)	3 (42.9)	1 (50.0)
Ever treated with non-givosiran medications, N (%)[d]	30 (32.3)	27 (32.1)	2 (28.6)	1 (50.0)
Hemin prophylaxis	23 (24.7)	21 (25.0)	1 (14.3)	1 (50.0)
Carbohydrate intake	5 (5.4)	4 (4.8)	1 (14.3)	0 (0)
IV glucose/dextrose	8 (8.6)	8 (9.5)	0 (0)	0 (0)
Other	5 (5.4)	4 (4.8)	0 (0)	1 (50.0)
History of iron overload[e], N (%)	17 (18.3)	16 (19.0)	0 (0)	1 (50.0)
Relatives with known or suspected AHP, N (%)	56 (60.2)	51 (60.7)	4 (57.1)	1 (50.0)
History of CKD[e], N (%)	18 (19.4)	17 (20.2)	1 (14.3)	0 (0)
History of liver disease[e], N (%)	10 (10.8)	7 (8.3)	1 (14.3)	2 (100.0)

[a]None of the enrolled patients had ALAD deficient porphyria (ADP). [b]Patients from sites in France do not have race reported, per country-specific regulatory guidance. [c]More than one test could be done for an individual patient. Data were not reported for 4 patients. [d]All reported medication records before data cutoff (May 19, 2023) are counted. No patients reported use of gonadotropin releasing hormone (GNRH) agonists. [e]Each of history of iron overload, history of CKD, and history of liver disease were not reported for 2 patients.

- The most frequently reported AHP symptoms at ELEVATE enrollment were pain, nausea, fatigue, tingling, numbness, weakness or paralysis, and anxiety (**Figure 3**)

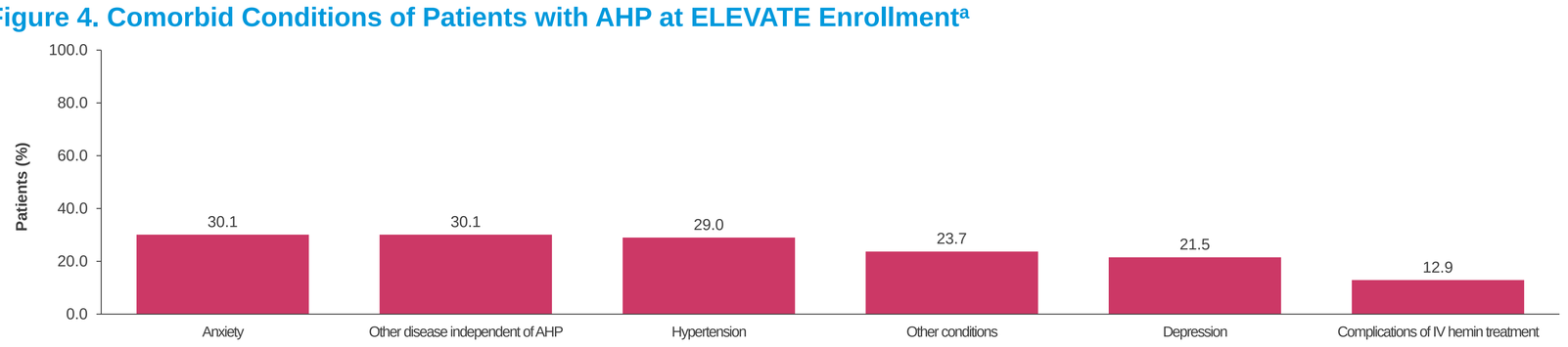
Figure 3. Most Common Symptoms of Patients with AHP at ELEVATE Enrollment[a]



[a]Percentages were based on the number of patients with AHP sign and symptom data (N=68) during the data-collection window (12 months prior to registry enrollment to 3 months after registry enrollment, irrespective of timing of givosiran treatment) and reflect results of assessment closest to registry enrollment date. Abdominal pain and back pain are subsets of any pain. Symptoms reported by >1 patient, but <20% overall included pain other than abdominal (chest, leg, muscle, other), constipation, high blood pressure, headache, breathing problems, urination problems, seizures, diarrhea, confusion, palpitations, seizures, and skin manifestations.

- The 3 most common comorbid conditions at enrollment were anxiety, other disease independent of AHP, and hypertension (**Figure 4**)

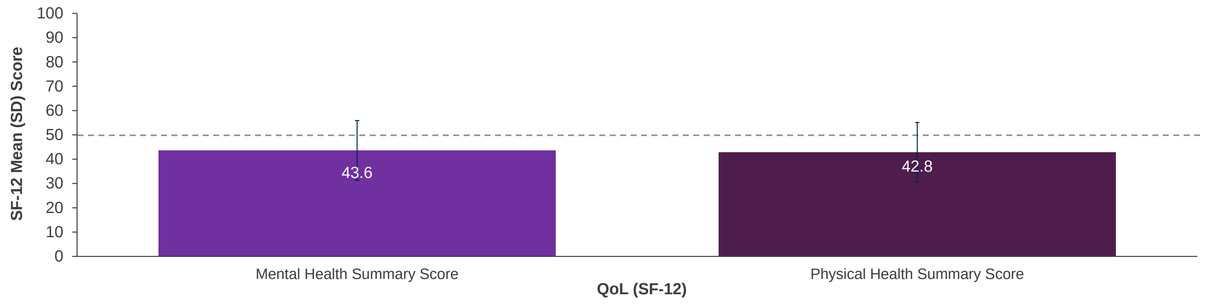
Figure 4. Comorbid Conditions of Patients with AHP at ELEVATE Enrollment[a]



[a]Comorbid conditions existing during data collection window (12 months prior to registry enrollment to 3 months after registry enrollment, irrespective of timing of givosiran treatment). Encephalopathy was reported by 3 patients (3.2%); no enrolled patients reported ascites comorbidity.

- QoL was assessed in 67/93 (72%) using the 12-item Short Form Health Survey (SF-12; range 0–100 points with higher scores indicating better physical and mental health functioning[1]) during the enrollment observation period most proximate to entry date (**Figure 5**)
  - US general population norms for SF-12 physical and mental health scores are both computed as 50 points[1]

Figure 5. QoL Assessed by SF-12 in Patients with AHP at ELEVATE Enrollment[a]



[a]Reflects assessment result closest to registry enrollment date during data collection window (12 months prior to registry enrollment to 3 months after registry enrollment, irrespective of timing of givosiran treatment). Dotted line represents US general population norms for SF-12 physical and mental health scores (both computed as 50 points). Error bars indicate standard deviations.

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Abbreviations: ADP, ALAD deficient porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; CKD, chronic kidney disease; GnRH, gonadotropin releasing hormone; HCP, hereditary coproporphyria; IV, intravenous; QoL, quality of life; SF-12, Short Form Health Survey; VP, variegate porphyria.
References: 1. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33. **2.** Puy H, Gouya L, Deybach JC. Porphyrias. *Lancet* 2010;375:924-37. **3.** Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: review and recent progress. *Hepatol Commun* 2019;3:193-206. **4.** Anderson KE, Lobo R, Salazar D, et al. Biochemical diagnosis of acute hepatic porphyria: updated expert recommendations for primary care physicians. *Am J Med Sci* 2021;362:113-21. **5.** Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. *Blood* 2012;120:4496-504. **6.** Puy H, Deybach JC, Lamoril J, et al. Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. *Am J Hum Genet* 1997;60:1373-83. **7.** Gouya L, Ventura P, Balwani M, et al. EXPLORE: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology* 2020;71:1546-58. **8.** Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N Engl J Med* 2020;382:2289-301. **9.** Kuter DJ, Bonkovsky HL, Monroy S, et al. Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial. *J Hepatol* 2023;Jul 19 Online Ahead of Print.

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