Enrollment Characteristics and Real-World Insights Into Disease Burden and Givosiran Treatment in Patients With Acute Hepatic Porphyria in the ELEVATE Registry

For US HCPs Only

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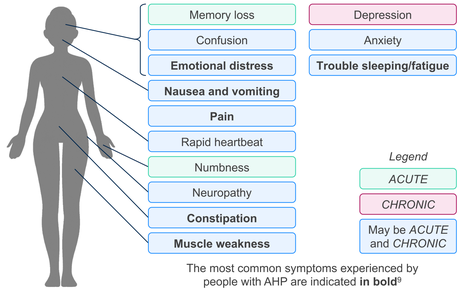
Conclusions

- Enrollment results from patients in the ongoing ELEVATE registry provide insights into patient characteristics and treatment patterns
- These results and continued data collection will inform subsequent analyses of the long-term safety and effectiveness of givosiran
- ELEVATE registry data underscore the heterogeneous nature of AHP and the substantial burden of comorbidities among affected patients
- As hematologists rarely encounter AHP, these findings will help enhance clinical understanding and management of AHP

Introduction

- AHP is a group of four rare, genetic, multisystemic disorders[1]:
  - AIP
  - VP
  - HCP
  - ADP
- Prevalence: symptomatic AHP diagnosed in ~1 per 100,000 people in Europe[2,3]
  - AIP is the least rare type of AHP, with a prevalence of ~1 per 1,600 Caucasian people[4]
- Patients with AHP can experience (**Figure 1**)[1,5-9]:
  - acute attacks
  - chronic symptoms
  - progressive elements
  - long-term complications

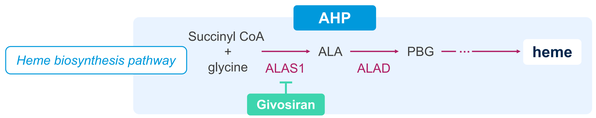
Figure 1. Acute and Chronic Symptoms of AHP[1,6-9]



The most common symptoms experienced by people with AHP are indicated **in bold**[9]

- AHP is caused by a defect in the heme biosynthesis pathway[1]
  - AIP: autosomal dominant mutations to *HMBS*
  - VP: autosomal dominant mutations to *PPOX*
  - HCP: autosomal dominant mutations to *CPOX*
  - ADP: autosomal recessive mutations to *ALAD*
- Givosiran is a small interfering RNA molecule that prevents accumulation of ALA and PBG in patients with AHP by silencing ALAS1 messenger RNA (**Figure 2**)[2,3]

Figure 2. AHP Pathway and Givosiran MOA



- Givosiran is approved in:
  - Brazil, Canada, Taiwan, and USA for treatment of AHP in adults[4,5]
  - EU, Japan, Switzerland, and UK for treatment of adults and adolescents (≥12 years old) with AHP[4-6]

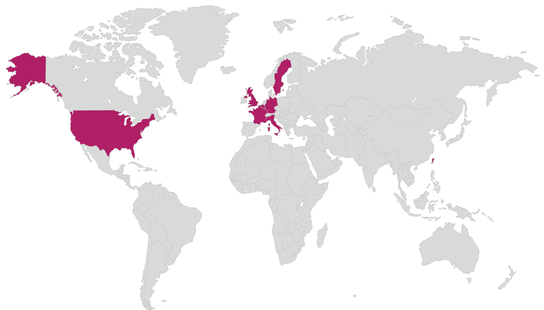
Objective

- ELEVATE (NCT04883905; **Figure 3**) is a global registry of patients with AHP created to:
  - characterize long-term, real-world safety of givosiran (primary objective)
  - characterize long-term, real-world effectiveness of givosiran
  - describe the natural history and clinical management of patients with AHP

Figure 3. ELEVATE Enrollment as of March 2025

- Initiated in April 2021
- Status: recruiting

217 enrolled patients[a]



28 sites activated in Belgium, France, Germany, Italy, Sweden, Switzerland, Taiwan, UK, and USA

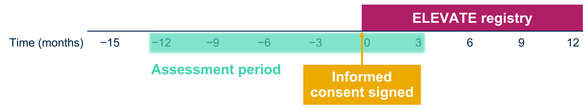
[a]Sites in Taiwan actively enrolling as of October 2024, data from Taiwan not included in this analysis.

Methods

- The data collection window (assessment period) for this analysis was defined as the period from 12 months before to 3 months after the informed consent form was signed (**Figure 4**)

Figure 4. Study Design

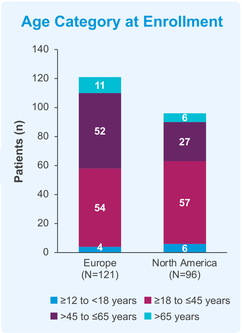
Inclusion criteria	Exclusion criteria
• Documented diagnosis of AHP per physician's determination • Signed patient consent form • In Germany, patients must be treated per the givosiran SmPC for the treatment of AHP[1]	• Current enrollment in a clinical trial for any investigational agent



Results

Table 1. Demographics Stratified by Region

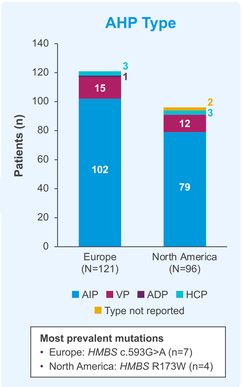
Demographic	Europe (N=121)	North America (N=96)
Age at enrollment, years, median (range)	47.0 (12-77)	40.5 (13-72)
Male, n (%)	25 (20.7)	12 (12.5)
Female – childbearing potential, n (%)	62 (51.2)	53 (55.2)
Female – non-childbearing potential, n (%)	34 (28.1)	31 (32.3)
Race, n (%)		
White	72 (59.5)	74 (77.1)
Black or African American	7 (5.8)	6 (6.3)
Asian	3 (2.5)	6 (6.3)
Other	0	2 (2.1)
Unknown	2 (1.7)	5 (5.2)
Not reported	16 (13.2)	3 (3.1)
Not collected[a]	21 (17.4)	0
Body mass index[b], kg/m^2, median (range)	23.4 (16.0-44.8)	26.0 (15.9-53.1)



[a]Patients from French sites do not have race reported per regulatory guidance; [b]Assessment result used was that closest to informed consent date during the enrollment period. Results were based on data cutoff date of March 24, 2025.

Table 2. Baseline Characteristics Stratified by Region

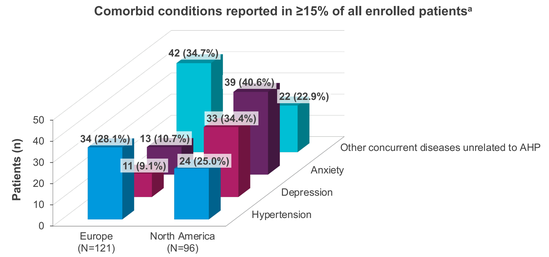
Characteristic	Europe (N=121)	North America (N=96)
Age at symptom onset, years, median (range)	29.0 (6-69)	27.5 (12-65)
Age at diagnosis, years, median (range)	29.5 (0-70)	28.5 (7-66)
Diagnostic test used for AHP diagnosis,[a] n (%)		
Genetic testing	81 (66.9)	67 (69.8)
PBG test	77 (63.6)	48 (50.0)
ALA test	62 (51.2)	40 (41.7)
Other biochemical testing	38 (31.4)	25 (26.0)
Fecal porphyrins	20 (16.5)	10 (10.4)
Relatives with known or suspected AHP, n (%)	82 (67.8)	61 (63.5)
History of iron overload, n (%)	14 (11.6)	8 (8.3)
History of liver disease, n (%)	10 (8.3)	9 (9.4)
History of chronic kidney disease, n (%)	24 (19.8)	9 (9.4)
ALA urine concentration, mmol/mol, mean (SD); n	2.5 (7.7); 75	1.8 (3.6); 29
PBG urine concentration, mmol/mol, mean (SD); n	3.8 (9.6); 79	5.0 (11.7); 27



Most prevalent mutations
- Europe: *HMBS* c.593G>A (n=7)
- North America: *HMBS* R173W (n=4)

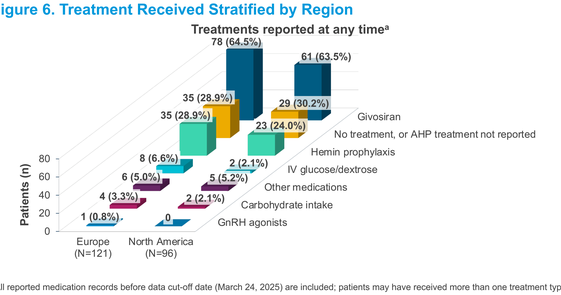
[a]More than one test may have been performed for each patient.

Figure 5. Baseline Comorbidities Stratified by Region



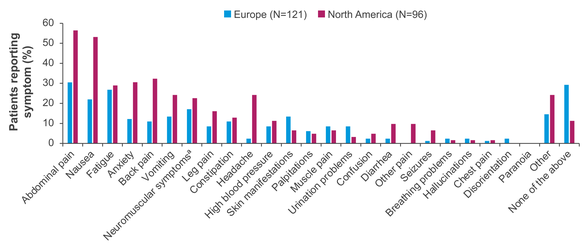
[a]Comorbid conditions as reported during the enrollment observation period.

Figure 6. Treatment Received Stratified by Region



[a]All reported medication records before data cut-off date (March 24, 2025) are included; patients may have received more than one treatment type.

Figure 7. Symptoms Reported During Assessment Period Stratified by Region



[a]Tingling, numbness, weakness and paralysis.
Percentage was calculated based on the number of patients who reported signs and symptoms: Europe (n=82), North America (62).

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Abbreviations: ADP, ALA dehydratase-deficiency porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; ALAD, ALA dehydratase; ALAS1, delta-aminolevulinate synthase 1; CoA, coenzyme A; GnRH, gonadotropin hormone-releasing hormone; HCP, hereditary coproporphyria; IV, intravenous; MOA, mechanism of action; N, total number of patients included; n, patients included per subgroup; PBG, porphobilinogen; SD, standard deviation; SmPC, summary of product characteristics; VP, variegate porphyria.

References: 1. Wang B, et al. *Hepatol Commun.* 2019;3:193-206. **2.** Silver S, et al. Presented at the American College of Gastroenterology Scientific Meeting, 25-29 October 2019, San Antonio, TX, USA. **3.** Wang B, et al. *Orphanet J Rare Dis.* 2022;17:327. **4.** Vassiliou D, et al. *J Intern Med.* 2022;291:81-94. **5.** Wang B. *Transl Gastroenterol. Hepatol* 2021;6:24. **6.** Simon A et al. *Patient.* 2018;11:527-37. **7.** Pischik E and Kauppinen R. *Appl Clin Genet.* 2015;8:201-14. **8.** Wheeden K et al. *Adv Ther.* 2022;39:4330-4345. **9.** Dickey A, et al. *JIMD Rep.* 2023;64:104-111.