Patient Demographics and Clinical Characteristics at Enrollment in ELEVATE, an International Registry of Acute Hepatic Porphyria

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Disclosures

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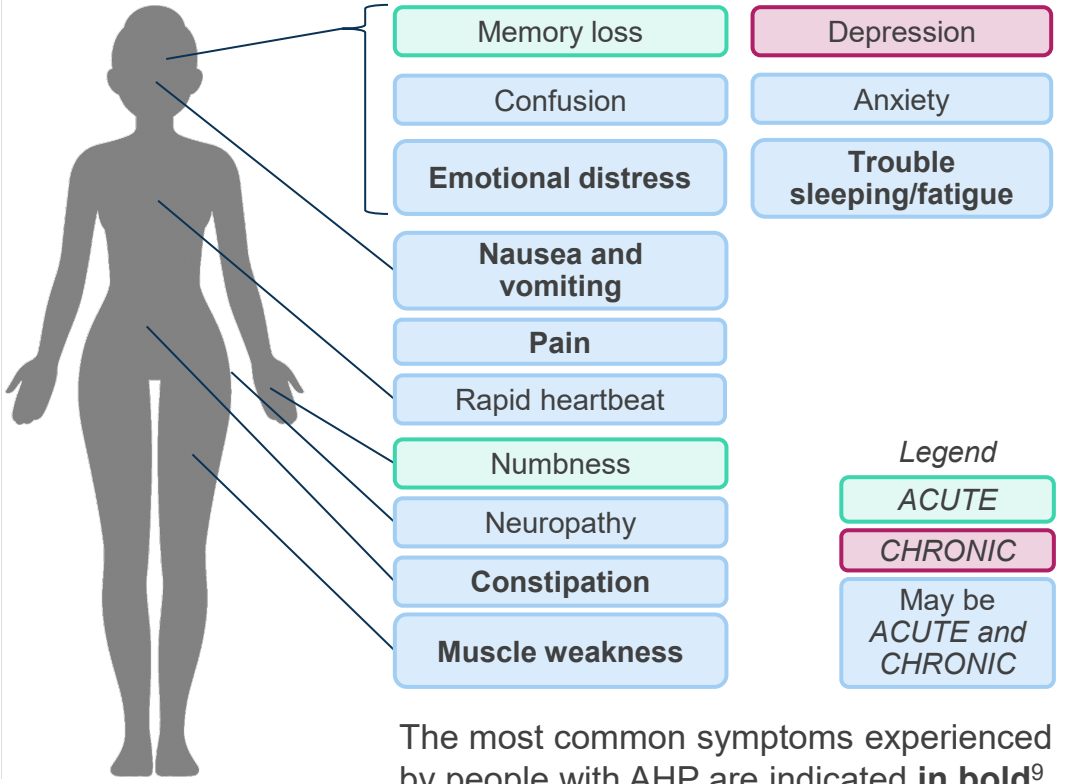
Introduction

- AHP is a group of four rare, genetic, multisystemic disorders[1]:
  - AIP
  - HCP
  - VP
  - 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[1,5,6]:
  - acute attacks
  - chronic symptoms
  - progressive elements
  - long-term complications

Acute and chronic symptoms of AHP[1,6-9]



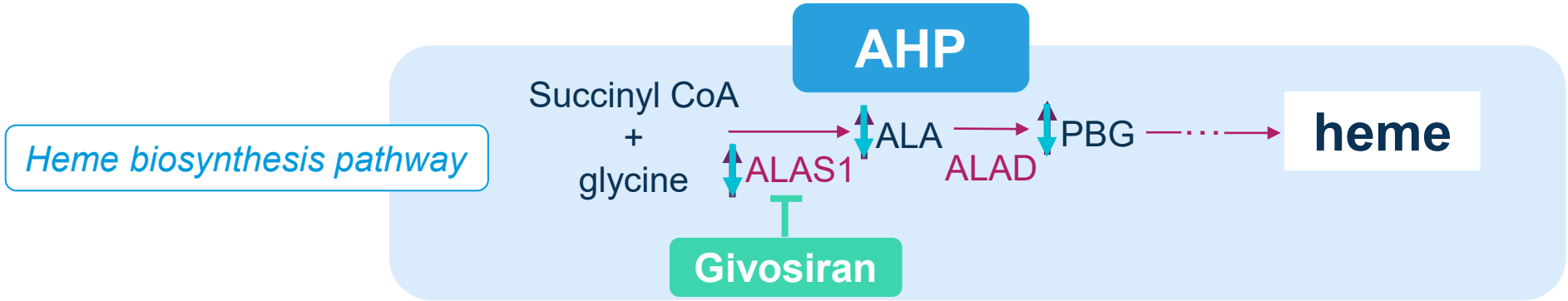
The most common symptoms experienced by people with AHP are indicated **in bold**[9]

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.

ADP, ALA dehydratase-deficiency porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; HCP, hereditary coproporphyria; VP, variegate porphyria.

Introduction (cont'd)

- 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[2,3]



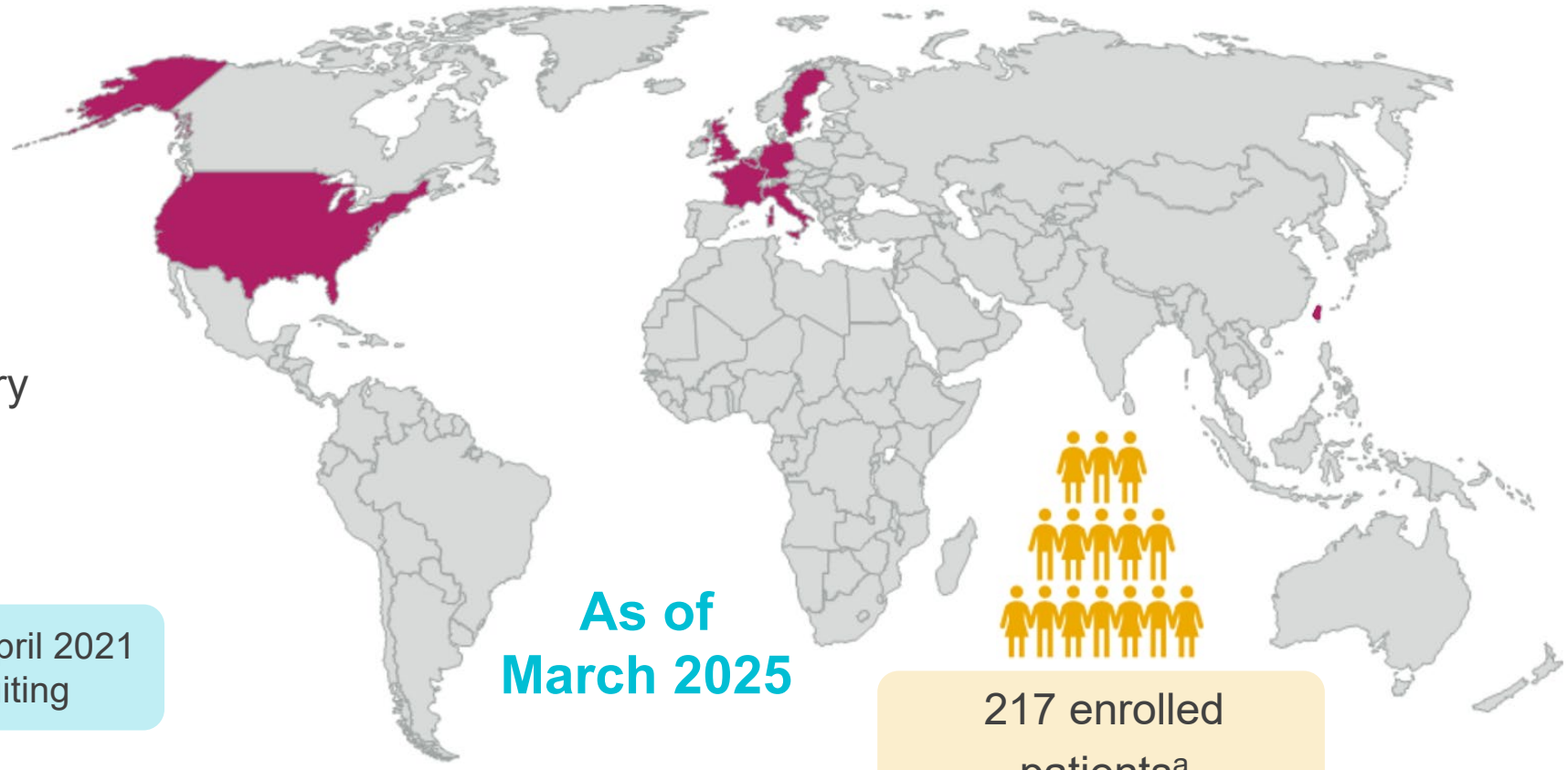
- Givosiran is approved in:
  - Brazil, Canada, Taiwan, and USA for treatment of AHP in adults[4,5]
  - EU, Japan, Switzerland, and UK for treatment of adults and adolescents (≥12 years old) with AHP[4-6]

1. Wang B, et al. *Hepatol Commun*. 2019;3:193-206. 2. Balwani M, et al. *N Engl J Med*. 2020;382:2289-2301. 3. Lazareth H, et al. *Kidney Int Rep*. 2021;6:1904-1911; 4. Dickey A, et al. *JIMD Rep*. 2023;64:104-111. 5. Lee M-J, et al. *J Formos Med Assoc*. 2024;123:678-686. 6. National Institute for Health and Care Excellence (NICE). https://www.nice.org.uk/guidance/hst16.

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; HCP, hereditary coproporphyria; PBG, porphobilinogen; VP, variegate porphyria.

Objective

- ELEVATE (NCT04883905) 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



As of March 2025

217 enrolled patients[a]

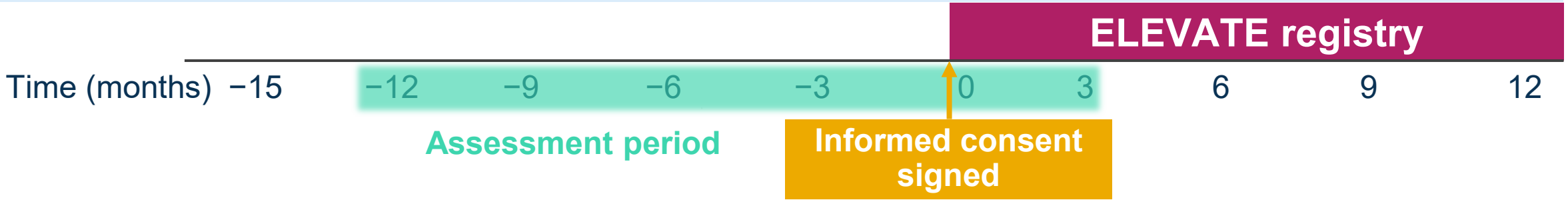
- Initiated in April 2021
- Status: recruiting

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.
AHP, acute hepatic porphyria.

Methods

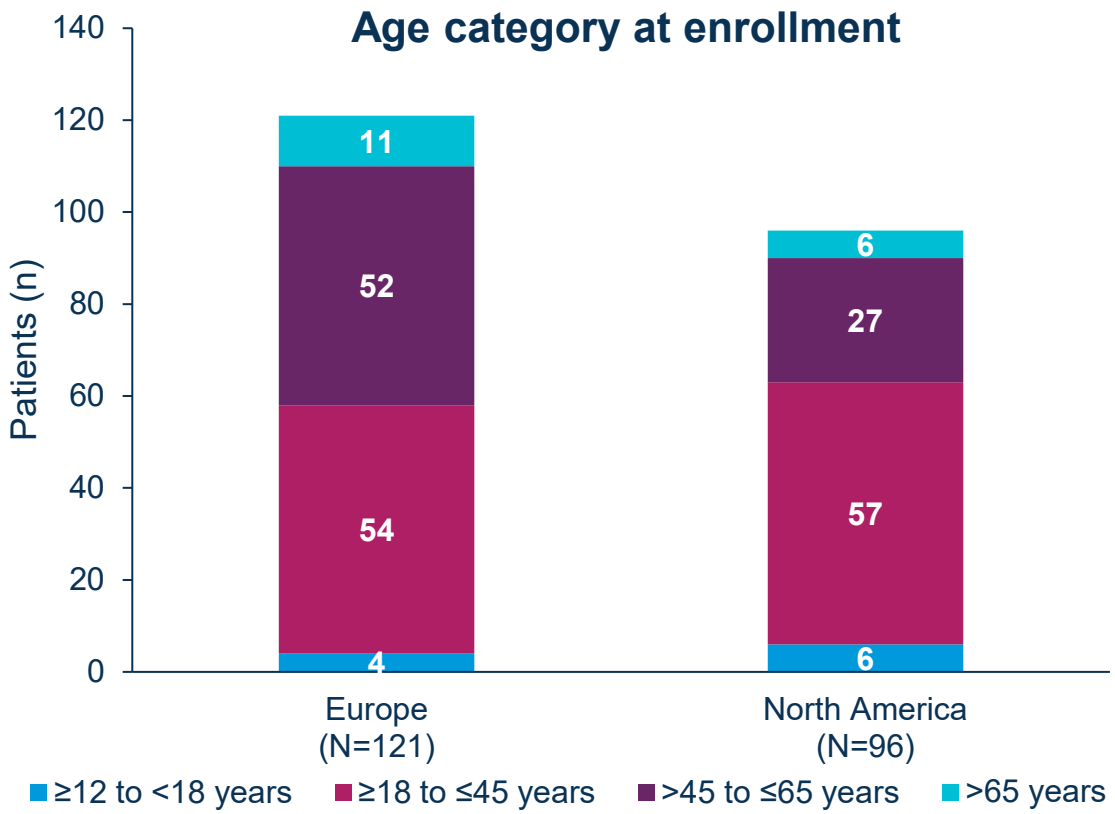
Inclusion criteria	Exclusion criteria
• Documented diagnosis of AHP per physician's determination • Signed patient consent form • In Germany, patients must be treated per the givosiran SmPC for the treatment of AHP[1]	• Current enrollment in a clinical trial for any investigational agent



- 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

1. Alnylam Netherlands B.V. SmPC, Givlaari. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (Accessed September 10, 2024).
AHP, acute hepatic porphyria; SmPC, summary of product characteristics.

Demographics Stratified by Region

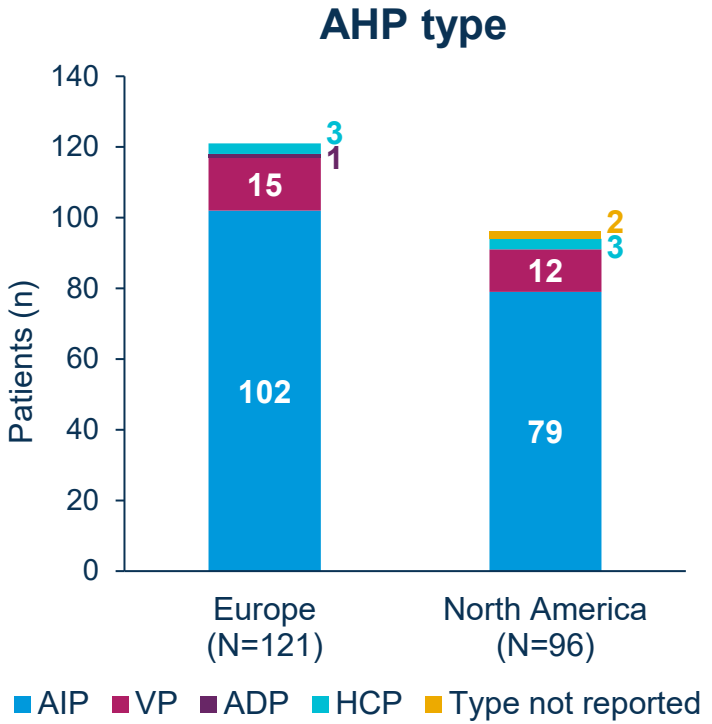


Demographic	Europe (N=121)	North America (N=96)
Age at enrollment, years, median (range)	47.0 (12-77)	40.5 (13-72)
Male, n (%)	25 (20.7)	12 (12.5)
Female – childbearing potential, n (%)	62 (51.2)	53 (55.2)
Female – non-childbearing potential, n (%)	34 (28.1)	31 (32.3)
Race, n (%)		
White	72 (59.5)	74 (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.
N, total number of patients included; n, patients included per subgroup

Baseline Characteristics Stratified by Region

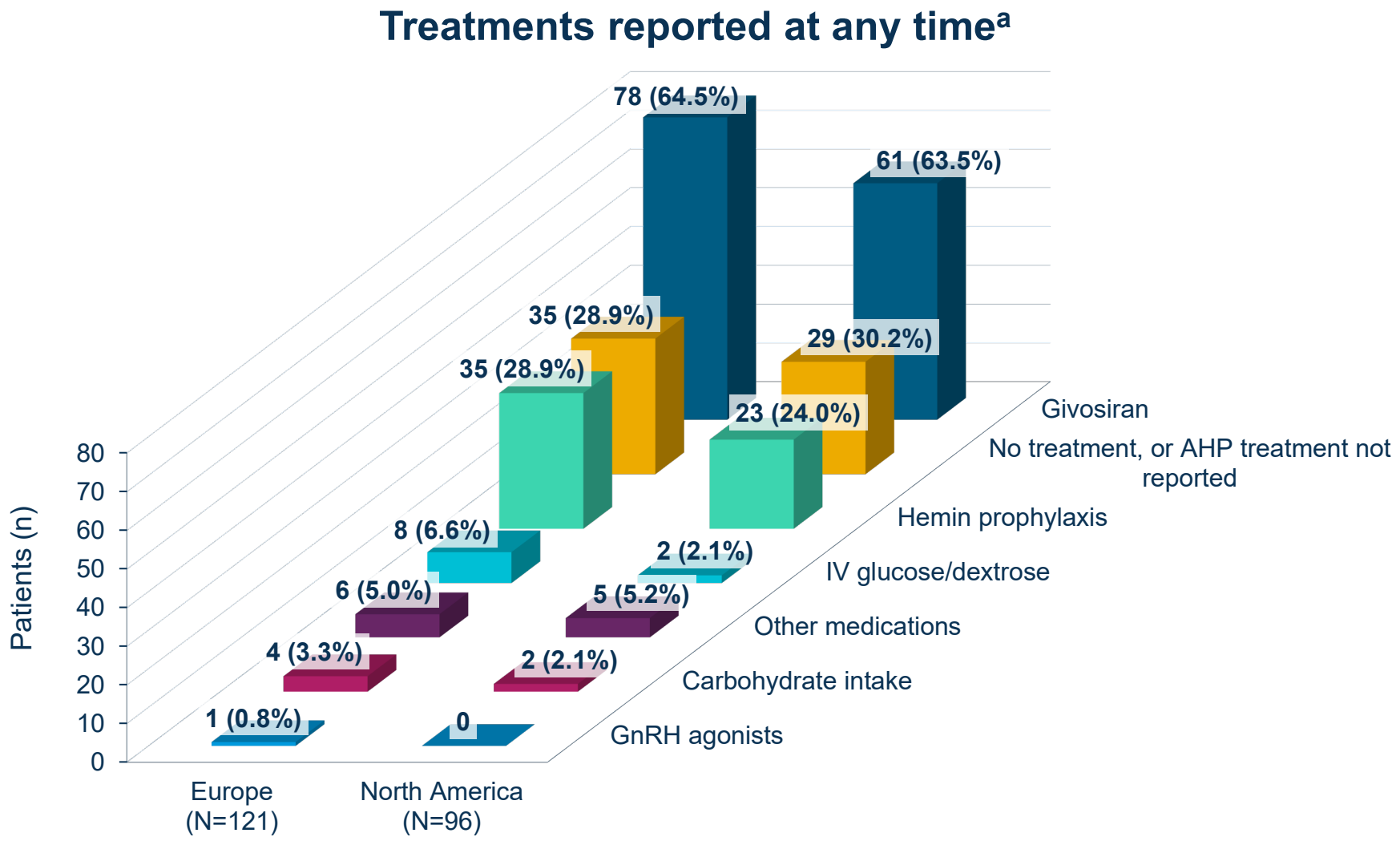
Characteristic	Europe (N=121)	North America (N=96)
Age at symptom onset, years, median (range)	29.0 (6-69)	27.5 (12-65)
Age at diagnosis, years, median (range)	29.5 (0-70)	28.5 (7-66)
Diagnostic test used for AHP diagnosis,[a] n (%)		
Genetic testing	81 (66.9)	67 (69.8)
PBG test	77 (63.6)	48 (50.0)
ALA 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)

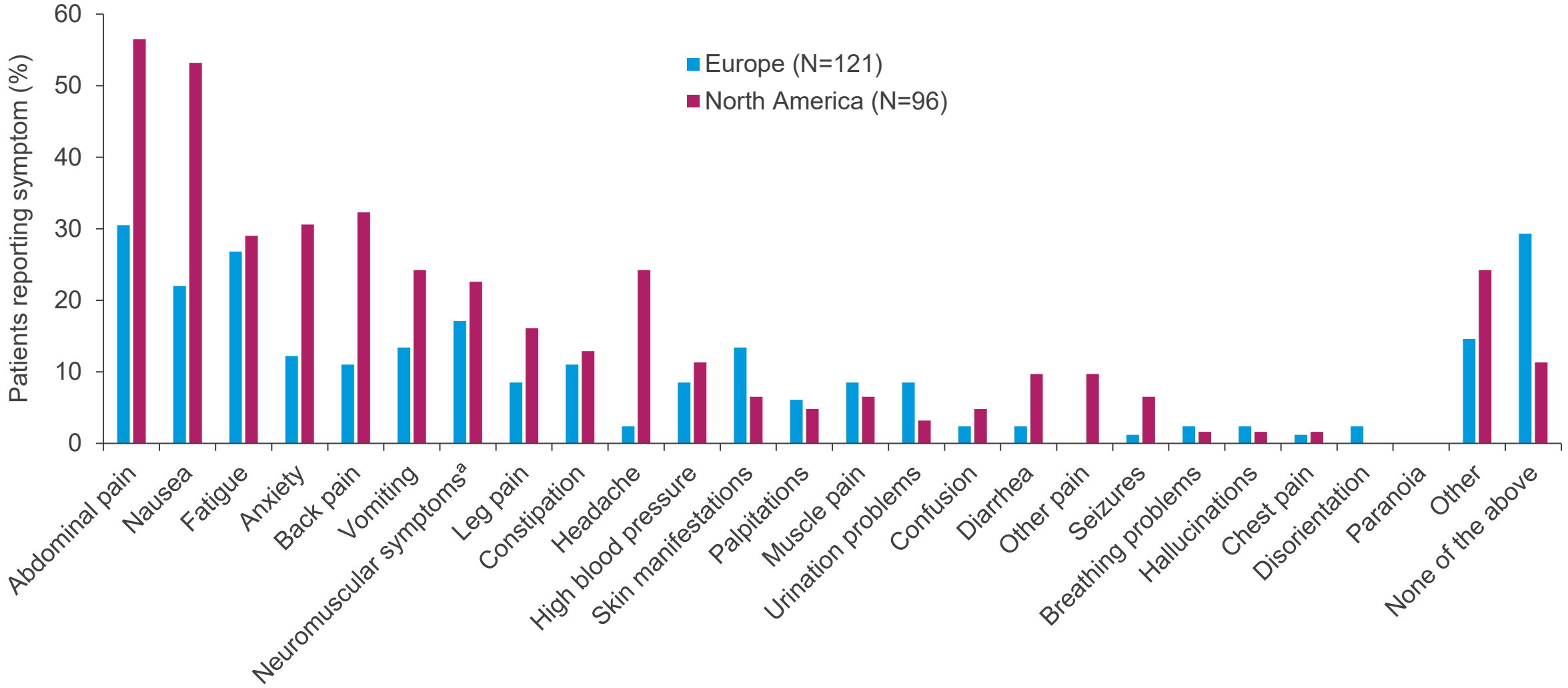
[a]More than one test may have been performed for each patient.
ADP, ALA dehydratase-deficiency porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; AHP, acute hepatic porphyria; HCP, hereditary coproporphyria; PBG, porphobilinogen; SD, standard deviation; VP, variegate porphyria.

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.
AHP, acute hepatic porphyria; GnRH, gonadotropin hormone-releasing hormone; IV, intravenous.

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).
N, total number of patients included.

Conclusions

- Baseline demographics and characteristics of patients enrolled in ELEVATE confirm the heterogeneous nature of AHP
- The ELEVATE registry is still in the recruitment phase
  - The registry is progressing well and is collecting a rich array of data for patients with and without treatment, and with a range of symptoms and comorbidities
  - Continued enrollment and follow-up are needed to collect sufficient data to assess safety and effectiveness endpoints
- Registry data collected will provide real-world evidence on the natural history and treatment of patients, helping to improve clinical management of AHP

AHP, acute hepatic porphyria.

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Thank You to the patients, their families, investigators, study staff, and collaborators for their participation in the ELEVATE registry