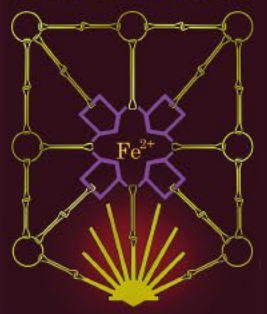
INTERNATIONAL CONGRESS OF PORPHYRINS AND PORPHYRIAS

ICPP 2024



September 21-25, 2024

Pamplona (Spain)

ipnet
INTERNATIONAL PORPHYRIA NETWORK

INTERNATIONAL CONGRESS OF PORPHYRINS AND PORPHYRIAS
ICPP 2024
September 21-25, 2024
Pamplona (Spain)
ipnet
INTERNATIONAL PORPHYRIA NETWORK

Patient demographics and clinical characteristics at enrolment in ELEVATE, an international registry of acute hepatic porphyria

Eliane Sardh,[1] David Cassiman,[2] Laurent Gouya,[3] Bruce Wang,[4] Weiming Du,[5] Teresa L Kauf,[5] Jamie L Weiss,[5] Manisha Balwani[6]

[1]Porphyria Centre Sweden, Centre for Inherited Metabolic Diseases, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [2]Department of Gastroenterology-Hepatology and Center for Metabolic Diseases, University Hospital Leuven, Leuven, Belgium; [3]Centre Français des Porphyries, Paris, France; [4]University of California, San Francisco, CA, USA; [5]Alnylam Pharmaceuticals, Cambridge, MA, USA; [6]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Disclosures

Eliane Sardh received grant support and personal fees, paid to Karolinska Institutet, from Alnylam Pharmaceuticals.
David Cassiman received consulting fees, advisory board fees, and lecture fees from Alnylam Pharmaceuticals.
Laurent Gouya received travel support and financial support from Alnylam Pharmaceuticals.
Bruce Wang is a scientific adviser to Alnylam Pharmaceuticals and Recordati Rare Diseases.
Weiming Du, **Teresa L Kauf**, and **Jamie L Weiss** are employees of and own stock and stock options in Alnylam Pharmaceuticals.
Manisha Balwani received grant support, consulting fees, advisory board fees, and lecture fees from Alnylam Pharmaceuticals; advisory board fees from Recordati Rare Diseases; grant support and advisory board fees from Mitsubishi Tanabe; and advisory board fees from Alexion, Genzyme/Sanofi, and Takeda.
In addition, Mount Sinai faculty are named co-inventors with Alnylam Pharmaceuticals on a patent related to the development of givosiran, the study drug. The Icahn School of Medicine at Mount Sinai receives payments related to this patent from Alnylam Pharmaceuticals, and a portion of these payments are also distributed to faculty and other co-inventors.

Funding
This study is funded by Alnylam Pharmaceuticals.
Acknowledgements
Under the direction of the authors, medical writing support was provided by Ester Baixauli PhD of Oxford PharmaGenesis, Oxford, UK, and was funded by Alnylam Pharmaceuticals.

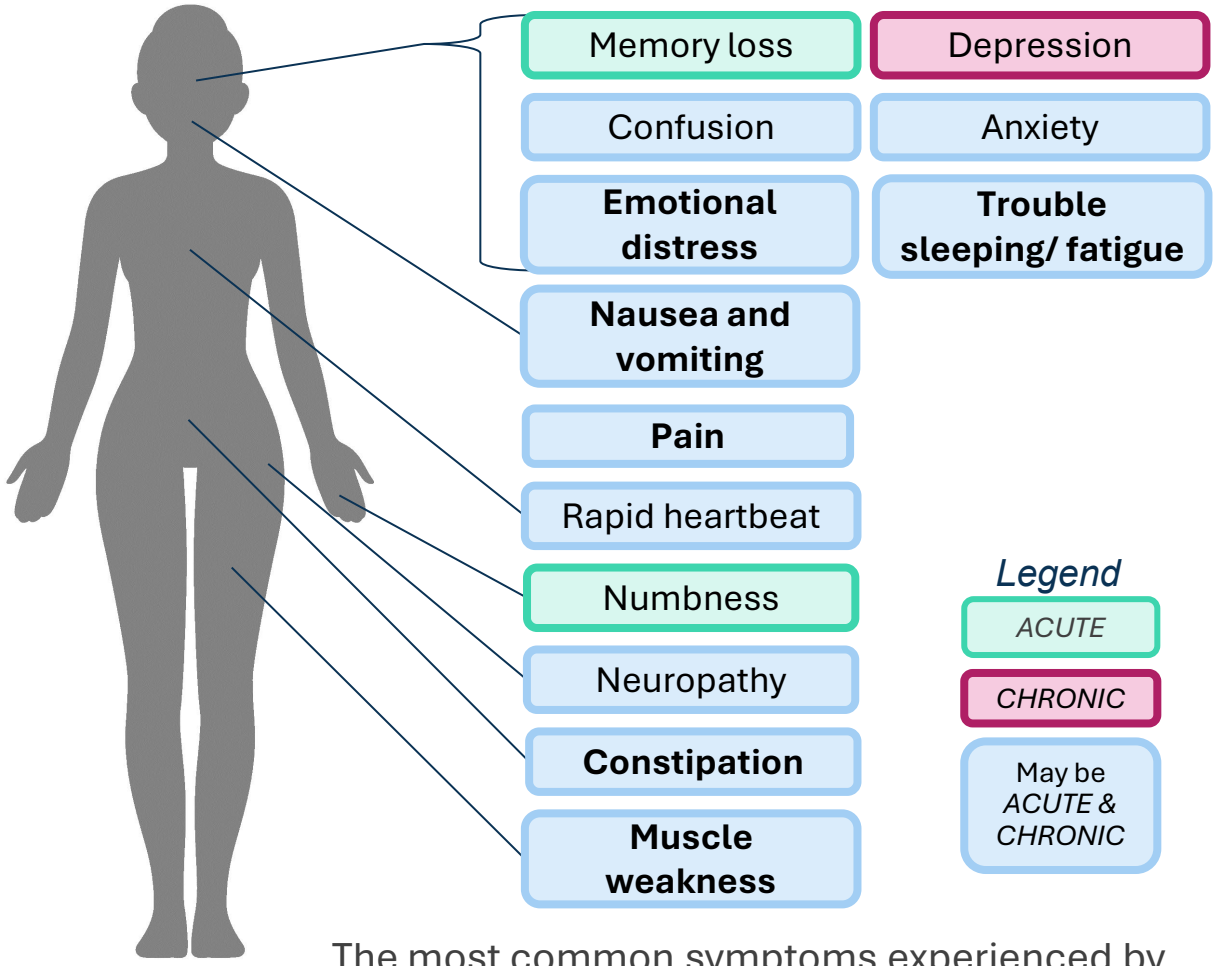
Scan this QR code to access a copy of the ELEVATE presentation on the Alnylam ICPP 2024 microsite

For US HCPs only
Scan to view congress materials

Background (1/3)

- 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]



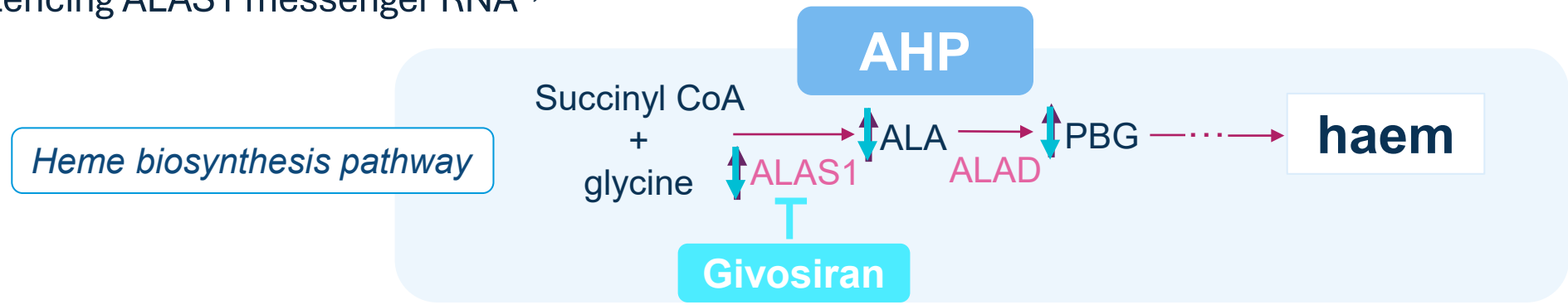
The most common symptoms experienced by people with AHP are indicated **in bold**[9]

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

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 and Sardh E. *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;39:4330-45; 9. Dickey A *et al. JIMD Rep* 2023;64:104-11

Background (2/3)

- AHP is caused by a defect in the haem 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]



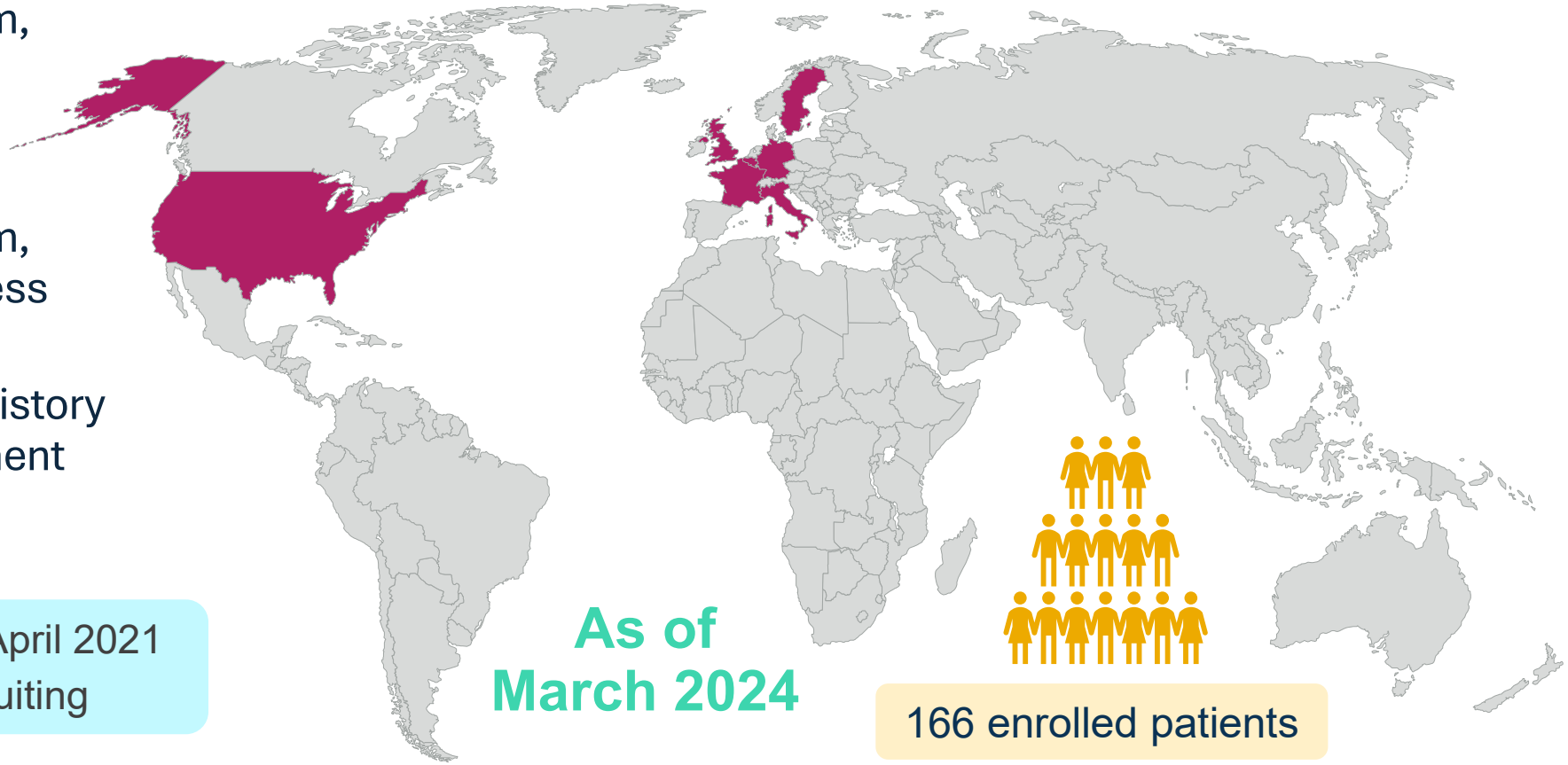
- Givosiran is approved in:
  - Brazil, Canada, Taiwan, and USA for treatment of AHP in adults[4,5]
  - EU, Japan, Switzerland, and UK for treatment of adults and adolescents (≥12 years old) with AHP[4–6]

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

1. Wang B *et al. Hepatol Commun* 2019;3:193-206; 2. Balwani M *et al. N Engl J Med* 2020;382:2289-301; 3. Lazareth H *et al. Kidney Int Rep* 2021;6:1904-11; 4. Dickey A *et al. JIMD Rep* 2023;64:104-11; 5. Lee M-J et al. *J Formos Med Assoc* 2024;123:678-86; 6. National Institute for Health and Care Excellence (NICE). 2021 HST16 (https://www.nice.org.uk/guidance/hst16)

Background (3/3)

- 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



- Initiated in April 2021
- Status: recruiting

As of March 2024

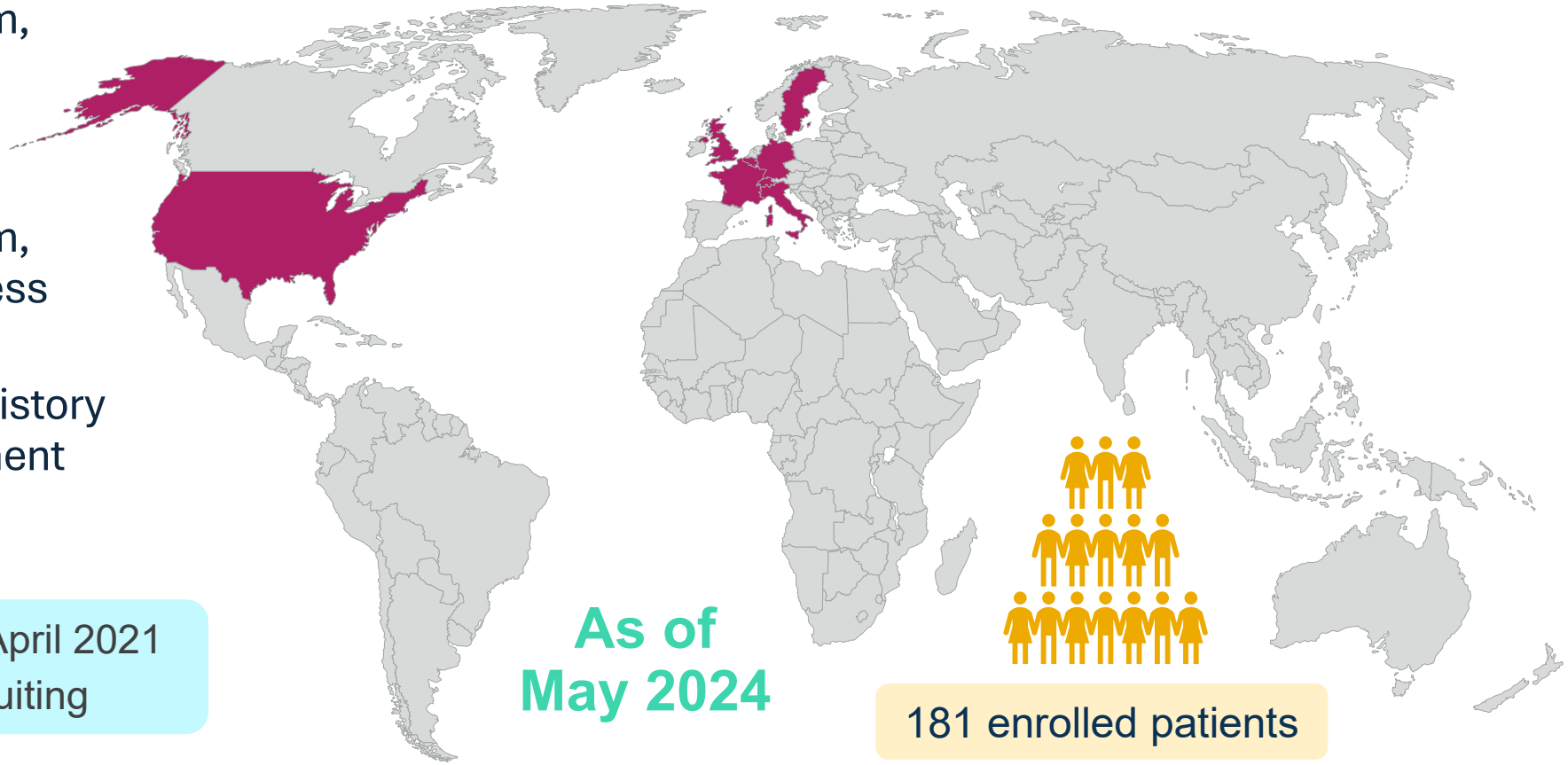
166 enrolled patients

25 sites activated in Belgium, France, Germany, Italy, Sweden, UK, and USA

AHP, acute hepatic porphyria

Background (3/3)

- 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



- Initiated in April 2021
- Status: recruiting

As of May 2024

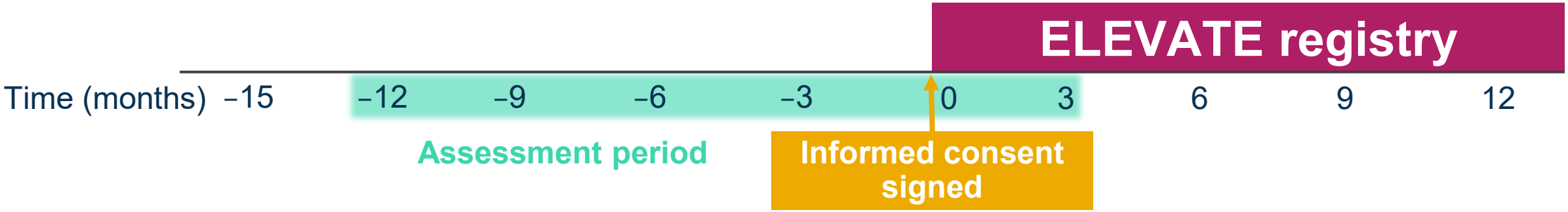
181 enrolled patients

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

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 enrolment in a clinical trial for any investigational agent

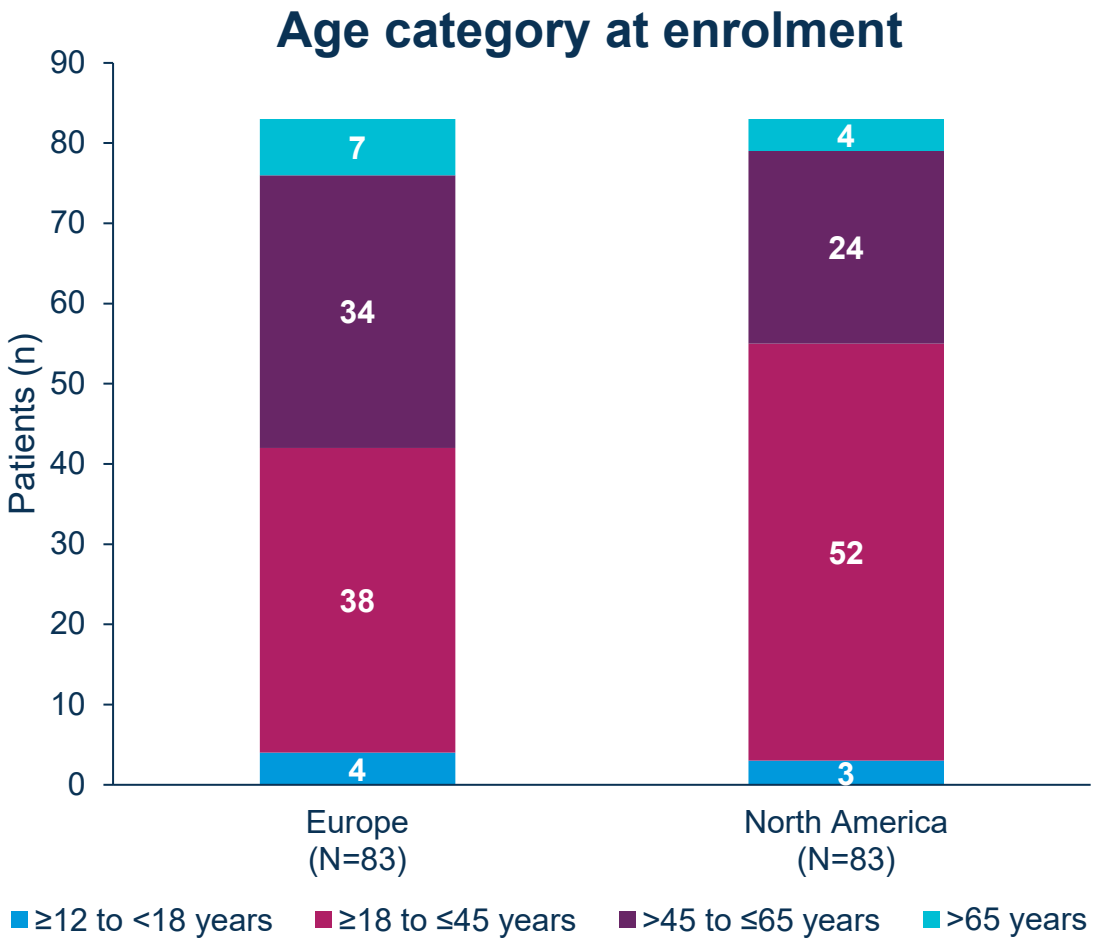


- The data collection window (assessment period) for this analysis was defined as the period from 12-months before to 3-months after the informed consent form was signed

AHP, acute hepatic porphyria; SmPC, summary of product characteristics

1. Alnylam Netherlands B.V. SmPC, Givlaari. European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (Accessed 10 September 2024)

Demographics stratified by region

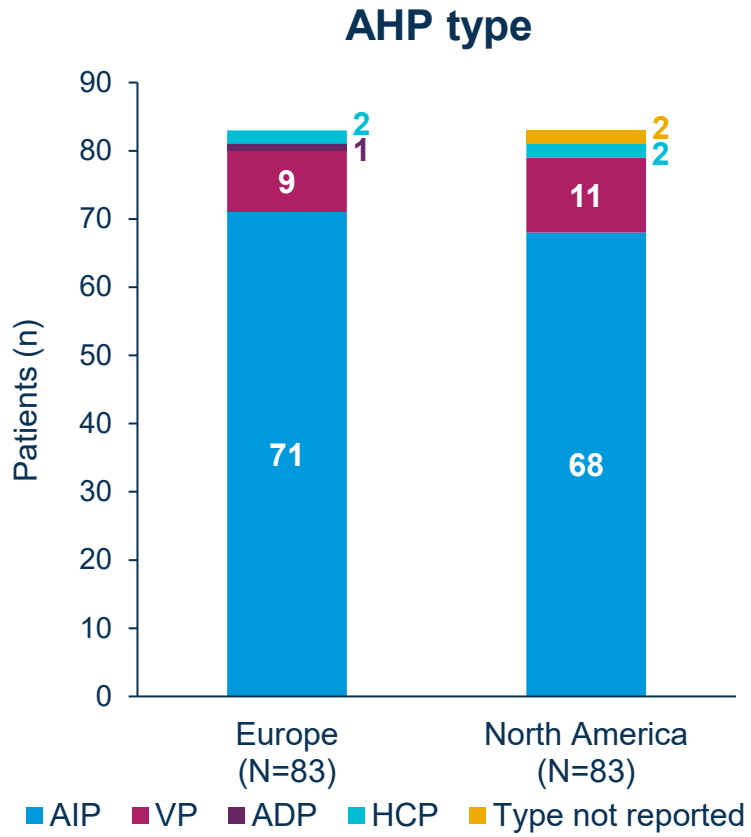


Demographic	Europe (N=83)	North America (N=83)
Age at enrolment, years, median (range)	45.0 (12-77)	41.0 (13-72)
Male, n (%)	20 (24.1)	11 (13.3)
Female – childbearing potential, n (%)	44 (53.0)	45 (54.2)
Female – non-childbearing potential, n (%)	19 (22.9)	27 (32.5)
Race, n (%)		
White	52 (62.7)	66 (79.5)
Black or African American	6 (7.2)	4 (4.8)
Asian	3 (3.6)	5 (6.0)
Other	0	1 (1.2)
Unknown	1 (1.2)	4 (4.8)
Not reported	1 (1.2)	3 (3.6)
Not collected[a]	20 (24.1)	0
Body mass index[b], kg/m^2, median (range)	23.8 (16.0-44.8)	26.1 (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 enrolment period
Results were based on data cutoff date of March 06, 2024
N, total number of patients included; n, patients included per subgroup

Baseline characteristics stratified by region

Characteristic	Europe (N=83)	North America (N=83)
Age at symptom onset, years, median (range)	30.0 (6-69)	28.0 (12-65)
Age at diagnosis, years, median (range)	31.0 (4-70)	28.5 (7-66)
Diagnostic test used for AHP diagnosis,[a] n (%)		
Genetic testing	60 (72.3)	57 (68.7)
PBG test	52 (62.7)	42 (50.6)
ALA test	39 (47.0)	34 (41.0)
Other biochemical testing	24 (28.9)	21 (25.3)
Faecal porphyrins	18 (21.7)	9 (10.8)
Relatives with known or suspected AHP, n (%)	51 (61.4)	53 (63.9)
History of iron overload, n (%)	13 (15.7)	8 (9.6)
History of liver disease, n (%)	8 (9.6)	9 (10.8)
History of chronic kidney disease, n (%)	19 (22.9)	8 (9.6)
ALA urine concentration, mmol/mol, mean (SD); n	7.8 (10.2); 18	2.3 (3.9); 23
PBG urine concentration, mmol/mol, mean (SD); n	10.8 (14.1); 18	6.7 (13.3); 20



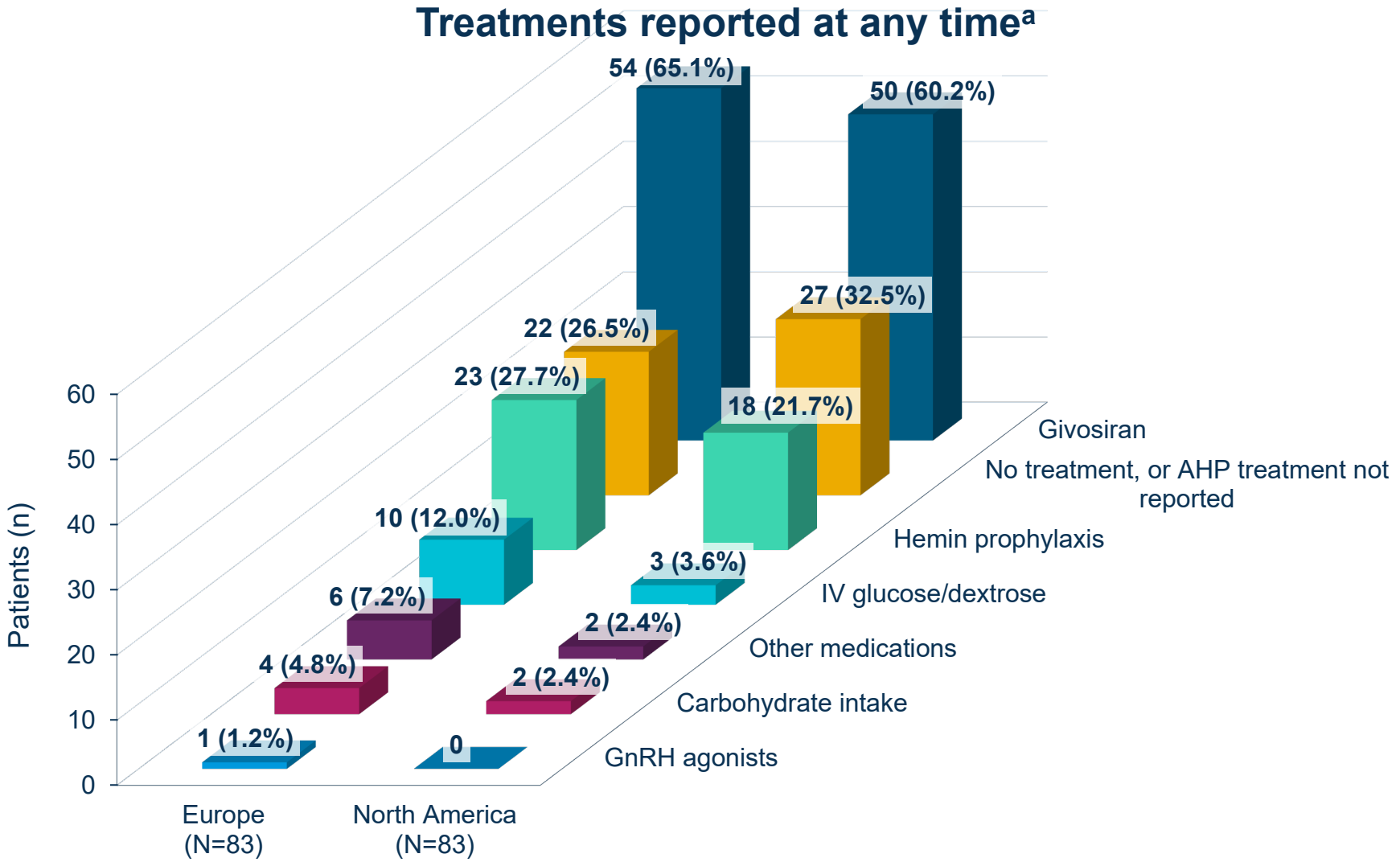
Most prevalent mutations

- Europe: *HMBS* Exon 9 (n=3)
- North America: *HMBS* R173W (n=5)

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

ADP, ALA dehydratase-deficiency porphyria ; AIP, acute intermittent porphyria; ALA, delta-aminolebulinic acid; AHP, acute hepatic porphyria; HCP, hereditary coproporphyria; N, total number of patients included; n, patients included per subgroup; PBG, porphobilinogen; SD, standard deviation; VP, variegate porphyria

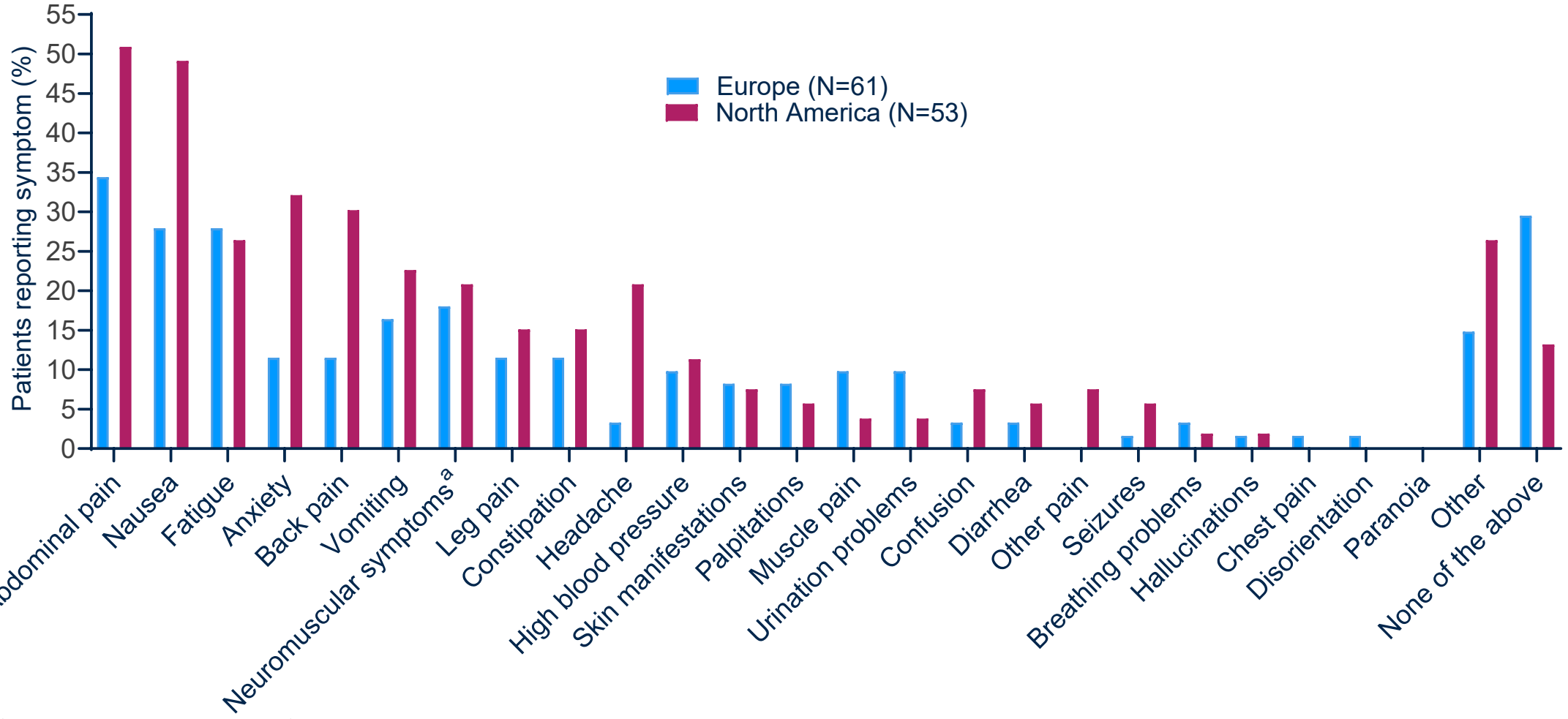
Treatment received stratified by region



[a]All reported medication records before data cut-off date (6 March 2024) are included; patients may have received more than one treatment type

AHP, acute hepatic porphyria; GnRH, gonadotropin hormone-releasing hormone; IV, intravenous; N, total number of patients included; n, patients included per subgroup

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
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 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 enrolment 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

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