

Acute Hepatic Porphyrria (AHP) Disease Manifestations and Daily Life Impacts in EXPLORE International Prospective, Natural History Study

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Acute Hepatic Porphyria (AHP)

Disease Overview¹⁻⁴

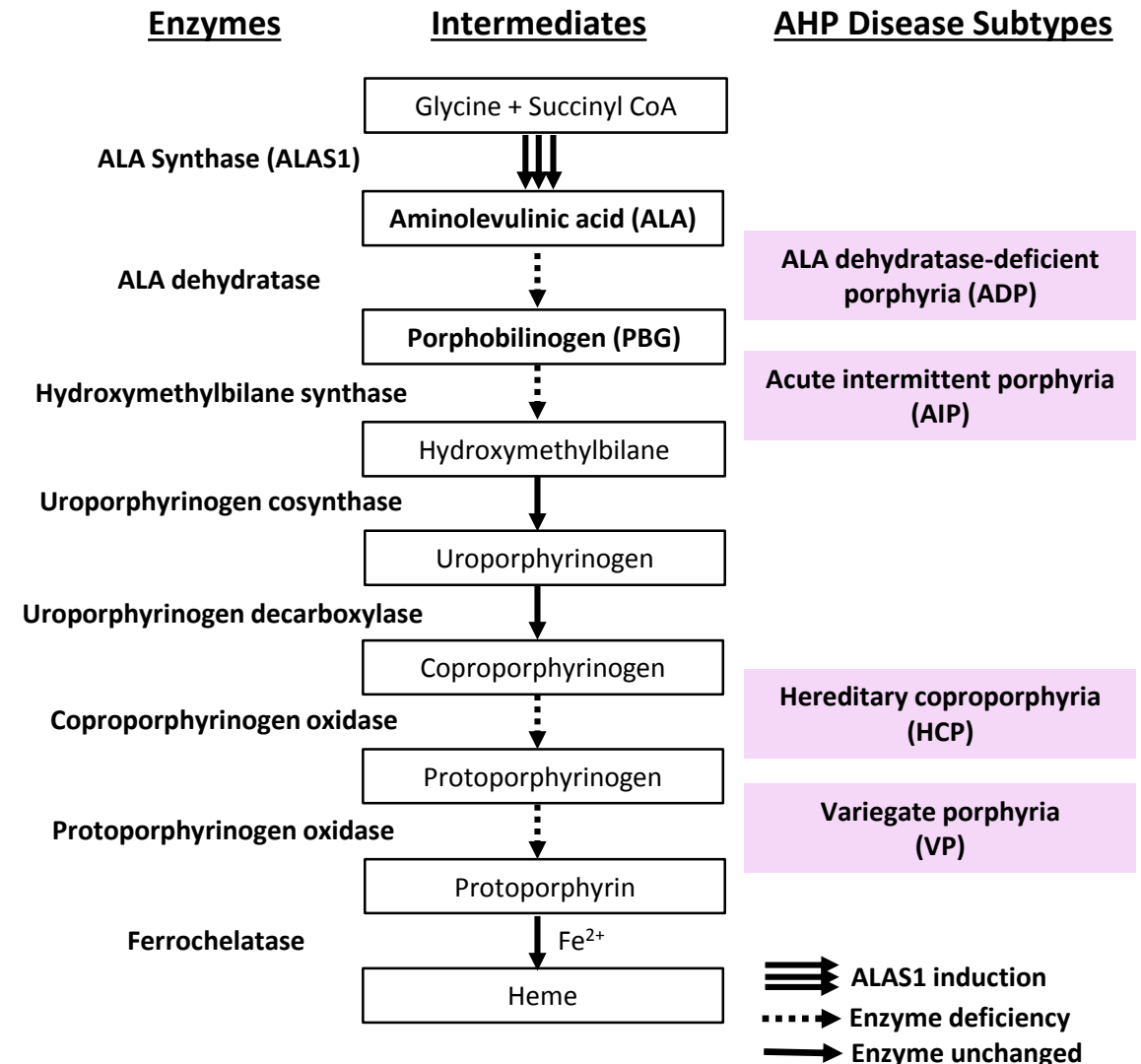
- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in liver
- Acute Intermittent Porphyria (AIP) most common, with mutation in hydroxymethylbilane synthase (HMBS)
- Additional types of AHP include hereditary coproporphyria (HCP) and variegate porphyria (VP) resulting from deficient levels of CPOX and PPOX enzymes, respectively

Disease Pathophysiology

- Induction of ALAS1 leads to accumulation of toxic heme intermediates ALA/PBG
- ALA believed to be primary toxic intermediate that causes disease manifestations

Attacks, Chronic Manifestations, and Comorbidities⁵⁻⁹

- Acute neurovisceral attacks can be life-threatening
- Chronic symptoms in between attacks increasingly recognized
- Hypertension, chronic kidney disease and liver disease
- Disability and social isolation common



1. Bonkovsky, et al., Am J Med. 2014;127:1233-41. 2. Elder, et al., JIMD. 2013;36:849-57. 3. Szlendak U et al. Adv Clin Exp Med. 2016;25:361-8. 4. Ramanujam VS, Anderson KE. Curr Protoc Hum Genet. 2015;86:1-26. 5. Pischik and Kauppinen. Appl Clin Genet. 2015;8:201-14. 6. Bonkovsky, et al., Poster. Presented at the American Association for the Study of Liver Diseases; November 9-13, 2018, San Francisco, CA, USA. 7. Stewart. J Clin Pathol. 2012;65:976-80. 8. Simon, et al., Patient. 2018;11:527-37. 9. Naik, et al., Mol Genet Metab. 2016;119:278-83.

explore **Natural History Study**

Study Design

- Observational, multinational, prospective natural history study

Key Eligibility Criteria

- Males or females ≥ 18 years old
- Diagnosis of AHP
 - Acute intermittent porphyria (AIP), hereditary coproporphyrin (HCP) and variegate porphyria (VP)
- Recurrent attacks
 - 3+ attacks[^] within 12 months of screening or using hemin or GnRH analog prophylactically

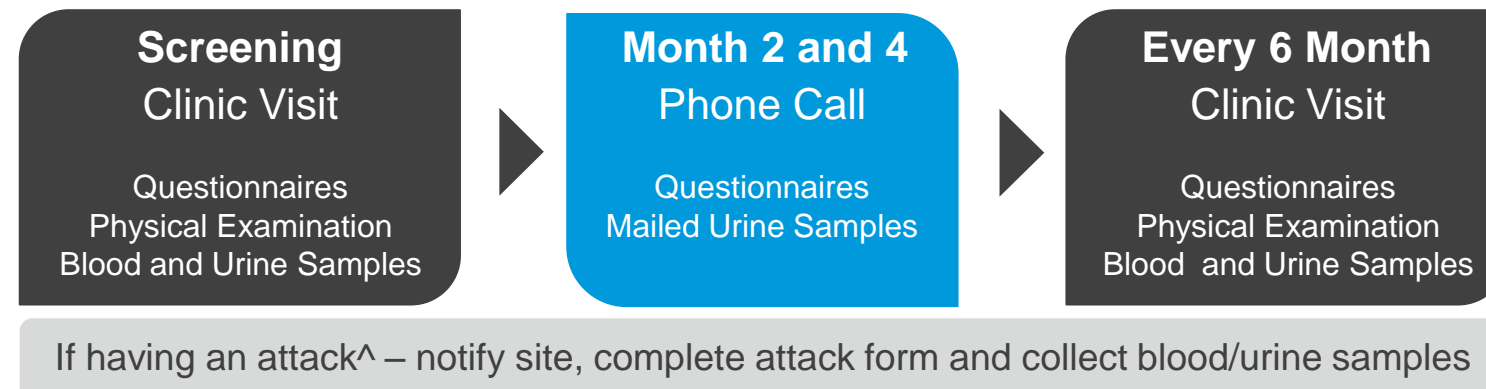
Key Objectives

- Characterize natural history and current AHP management
 - Medical history and medication usage
 - Porphyrin signs and symptoms
 - Biomarkers
 - Quality of life (QoL)

Part B ongoing and enrolling patients

- Eligibility criteria expanded to ≥ 1 attacks[^] within 12 months of screening
- Phone call every 3-6 months for 3 years; no clinic visits required

Part A Assessments



[^]Attacks defined as acute porphyria symptoms requiring increase in treatment (hemin, pain medications, carbohydrates) or hospitalization
ClinicalTrials.gov Identifier: NCT02240784; GnRH, Gonadotropin-releasing hormone

Patient Demographics and Baseline Characteristics

- 112 patients, 13 countries (44% US), median follow-up 12 months (range: 9-12 months)
- Most patients were white/Caucasian females with AIP

Characteristic	EU (n=63)	US (n=49)
Mean age, years	41 (13)	37 (12)
Female, n (%)	55 (87)	45 (92)
Race, n (%)		
White/Caucasian	52 (83)	43 (88)
Asian	0	3 (6)
Black/African American	0	3 (6)
Not answered	11 (18)	0
Height, cm	166	165
BMI, kg/m ²	24	26
AHP subtype, n (%)		
Acute intermittent porphyria	61 (97)	43 (88)
Variegate porphyria	2 (3)	3 (6)
Hereditary coproporphyrin	0	3 (6)

Data are mean (SD) unless otherwise stated
AHP, acute hepatic porphyria; BMI, body mass index; SD, standard deviation

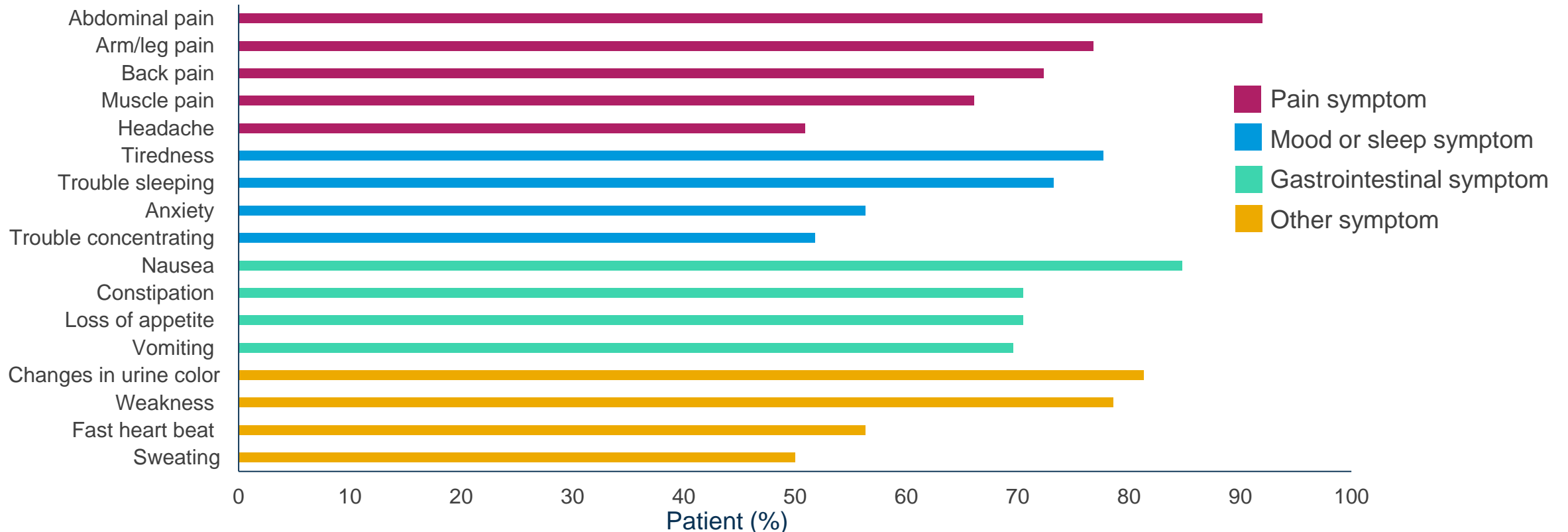
Attack Frequency and Common Attack Symptoms at Baseline

- Mean (S.) attack number in prior 12 months of 9.0 (10.6) for EU patients and 9.7 (9.2) for US patients
 - ~35% of attacks required hospitalization, with similar rate in EU and US (3.2 and 3.5, respectively)
- Abdominal pain most prominent symptom experienced during attacks

Patient Questionnaire: “Symptoms that are always or usually associated with a porphyria attack”

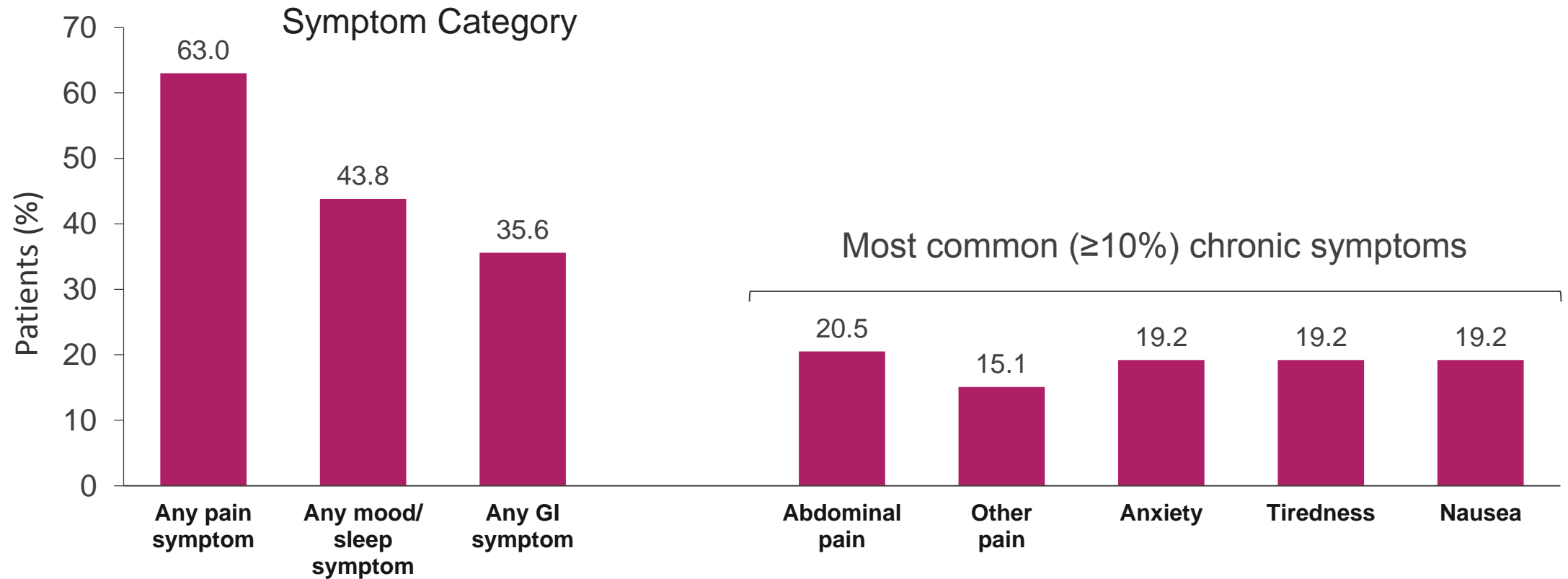
(n=112)¹

(reported by ≥50% of patients)



Patient-reported Chronic Symptoms at Baseline

- Chronic symptoms between attacks reported by 65% (n=73/112) of patients; occurred more frequently in US than EU patients (71.4% and 60.3%, respectively)
- Among patients with chronic symptoms, 71% (n=52/73) reported daily¹ symptoms
- Similar to porphyria attacks, most common chronic symptom was pain



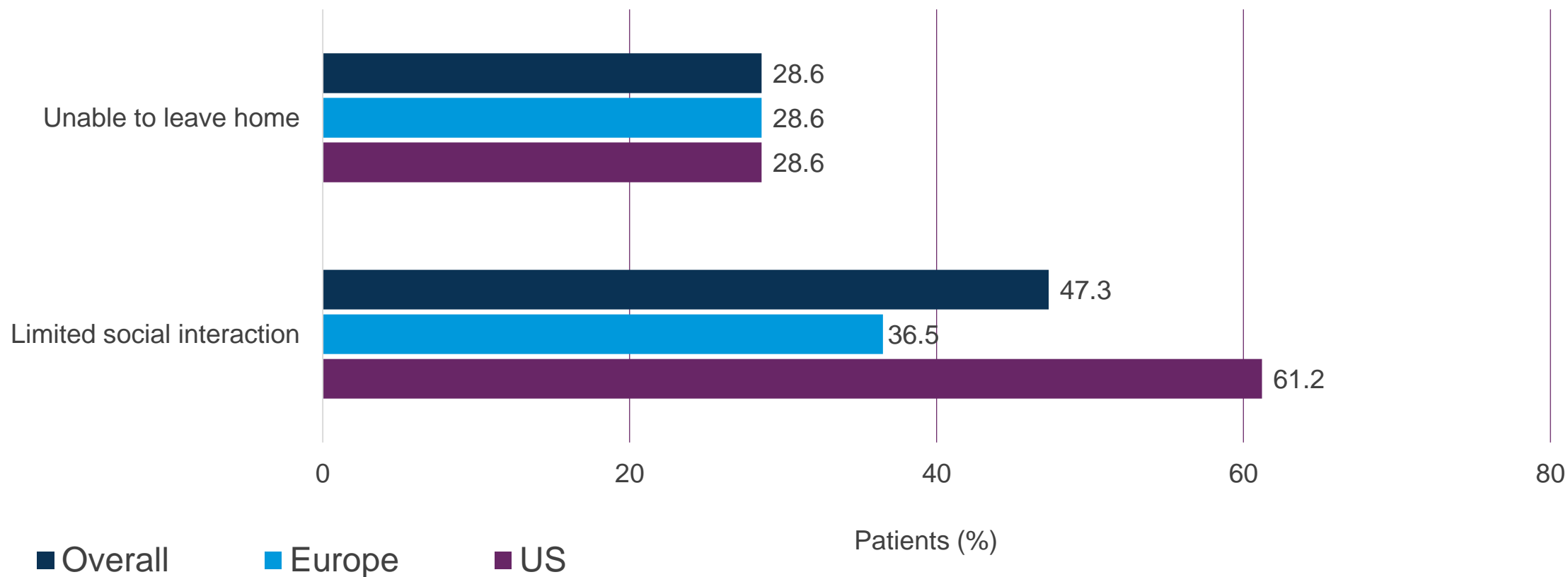
1. Gouya L et al. Oral presented at *EASL* 2018. 2. Ventura P et al. Poster presented at *EASL* 2019.

Chronic symptoms are those occurring during asymptomatic periods

Impact of Disease on Daily Life at Baseline

Disease-Related Social Limitations

- 28.6% of both EU (18/63) and US patients (14/49) reported being home-bound
- 36.5% of EU patients (23/63) and 61.2% of US patients (30/49) had limited social interactions in the prior 12 months

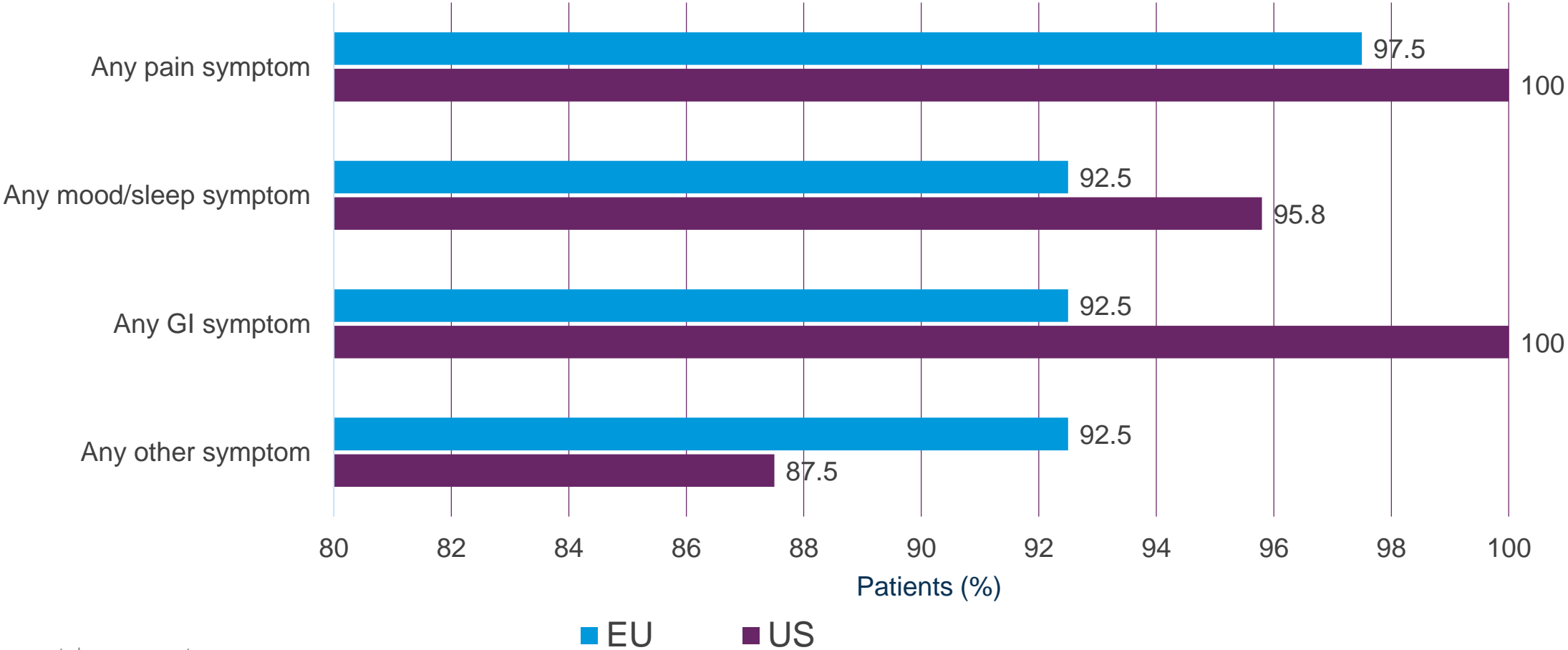


Percentages are calculated as a proportion of total EU patients (n=63) and US patients (n=49) included in the study
EU, Europe; US, United States

On-Study Symptoms During Attacks

Attack Symptoms

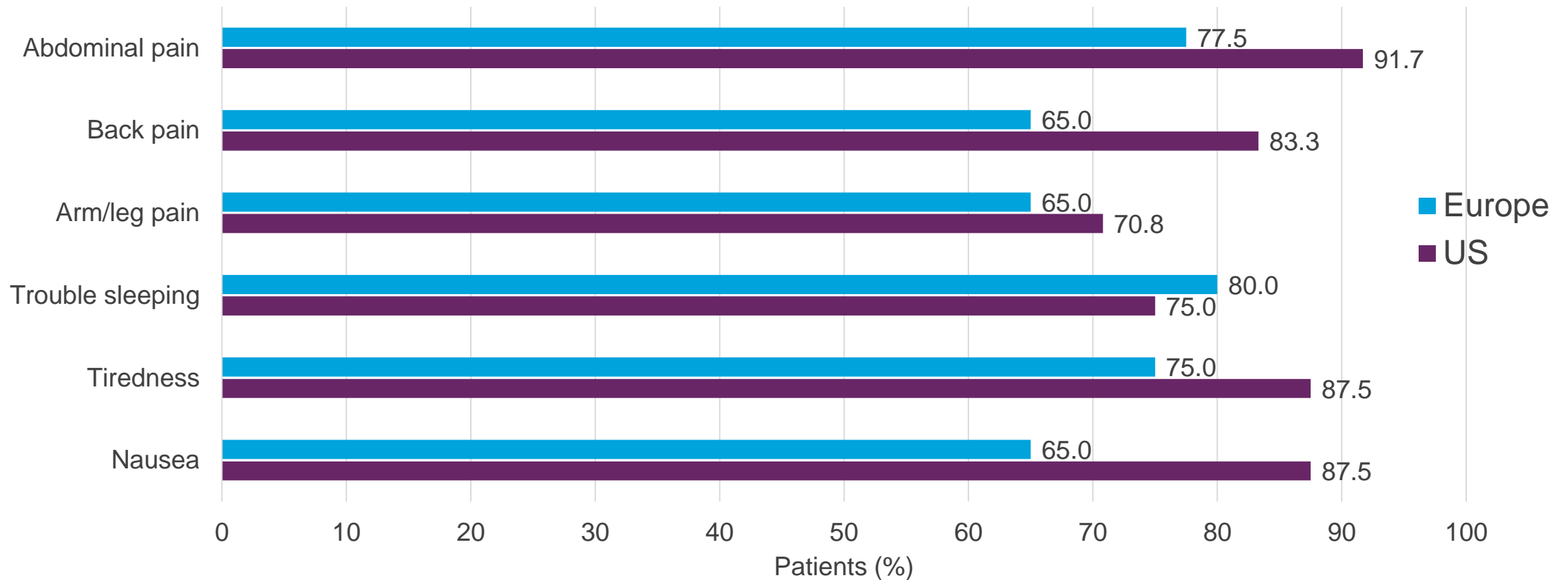
- During attacks on study, patients in EU and US reported similar symptom constellations



Patients are counted once per symptom
Percentages are calculated based on n=40 EU respondents and n=24 US respondents
EU, Europe; US, United States

Commonly (>70%) Reported Symptoms During Attacks

- **Abdominal pain most common attack symptom**
 - Other pain symptoms: muscle (EU: 47.5%; US: 66.7%), headache (EU: 45.0%; US: 62.5%), skin (EU: 22.5%; US: 29.2%), and other pain (EU: 25.0%; US: 33.3%)
- **In general, a greater proportion of US patients reported attack symptoms than EU patients**



Patients are counted once per symptom. Symptoms were included if >70% of overall EU and US reported it. Percentages are calculated based on n=40 EU respondents and n=24 US respondents.

Summary

Baseline Characteristics

- Overall, patients with AHP experiencing ongoing attacks in the EU and US showed similar attack rates and similar symptoms in the acute and chronic setting
 - Most common attack symptoms included pain (abdomen, back, or arm/leg), nausea, change in urine color and tiredness
 - Most common chronic symptoms included pain, anxiety, tiredness and nausea
- Patients reported negative impacts on daily life from AHP, including limited social interactions and being home-bound

On Study Results

- This study demonstrates that a large proportion of patients with AHP experiencing ongoing attacks in the EU and the US have chronic symptoms that likely also contributes to their impaired daily functioning

Next Steps

EXPLORE Part B is ongoing in 22 active sites, 13 countries with ~100 patients

- Expanding to more countries and broader patient population (e.g., ≥ 1 attacks within prior 12 mo, adolescents, ADP patients)

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