EXPLORE: A Prospective, Multinational Natural History Study of Acute Hepatic Porphyria Patients with Recurrent Attacks

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Abstract

Introduction: The acute hepatic porphyrias (AHP), including acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are due to a deficiency in the liver of one of the eight enzymes required for heme biosynthesis. Induction of the first enzyme 5-aminolevulinic acid synthase 1 (ALAS1) by triggers such as fasting or drug exposure can lead to accumulation of neurotoxic heme intermediates that result in acute life threatening neurovisceral attacks.

Methods: We are currently performing a prospective, multinational, observational study to characterize the natural history and clinical management of patients with AHP who experience recurrent attacks (≥ 3 attacks per year) or receive prophylactic treatment to prevent attacks. Patient porphyria disease activity questionnaires, physical examinations, plasma and urinary porphyrin precursors, circulating ALAS1 mRNA and health care utilization data are collected at pre-specified intervals throughout the 6 month study. In addition, porphyria attack assessments and porphyrin precursor levels are collected during attacks.

Interim Results: Enrollment is complete, and the study is ongoing. A total of 112 patients have been enrolled from 20 centers in 13 countries. The mean patient age is 39 years old, with the majority being female (100F; 12M) and having a diagnosis of AIP (AIP=104; HCP=3; and VP=5). Less than half of the patients (38%) reported taking heme prophylactically to prevent attack s. Patients reported a mean of 9.5 attacks (median 6; range 0-54) in the prior year. The most common acute attack symptoms included abdominal pain (92%), nausea (84%), vomiting (69%) and weakness (79%). Symptoms similar in character to those occurring in attacks were reported chronically (i.e. all the time) in 46% of the patients. The baseline urinary porphobilinogen and aminolevulinic acid levels while patients were not having an acute attack were elevated at 30.6 mmol/mol Cr and 29.6 mmol/mol Cr respectively (upper limit of normal: PBG < 1.2 mmol/mol Cr; ALA < 3.1 mmol/mol Cr).

Summary: This ongoing study should provide important information about the full spectrum of disease in AHP patients with recurrent attacks, as well as provide insights into AHP pathophysiology and disease management. The fact that close to half the patients have porphyria symptoms all the time, even when not in the setting of an acute attack, suggests the disease is more chronic than previously appreciated. Additional 6-month data from this study will be reported.

Acute Hepatic Porphyria Disease Overview

Acute Hepatic Porphyria (AHP)[1,2]

- Inborn errors of heme synthesis from liver enzyme defects
- AIP most common, with prevalence 2-5 per 100,000, approximately 5-10% manifest
  - Autosomal dominant mutation in hydroxymethylbilane synthase (HMBS)

Disease Pathophysiology

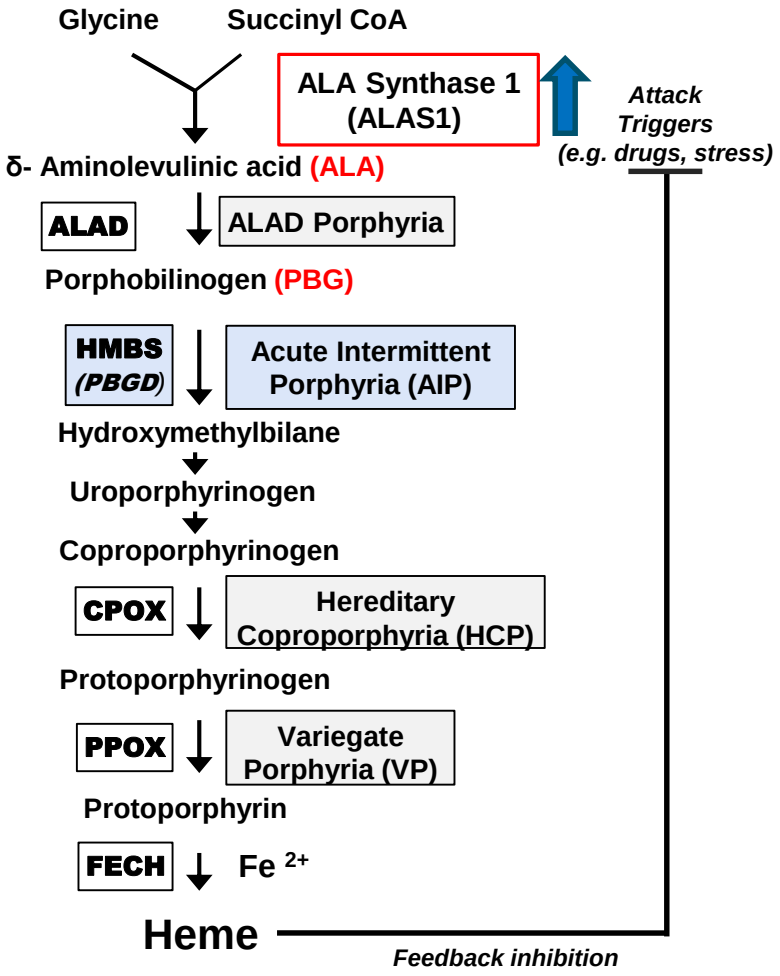
- Increased ALAS1 levels leads to accumulation of toxic heme intermediates ALA/PBG that cause acute attacks

Attack Manifestations

- Autonomic Nervous System
  - Severe abdominal pain, hypertension
- Central Nervous System
  - Mental status changes, seizures
- Peripheral Nervous System
  - Muscle weakness, paralysis

Treatment and Unmet Need

- Acute treatment and prophylaxis with human hemin (IV)
- Unmet need for more efficacious and safer therapies for prophylaxis



*Attacks defined as acute porphyria symptoms requiring increase in treatment (heme, pain medications, carbohydrates) or hospitalization

[1]Bonkovsky HL, et al. Am J Med. 2014;127(12):1233-41; [2]Elder G, et al. J Inherit Metab Dis. 2013;36(5):849-57.

explore Study Design Overview

Study Design

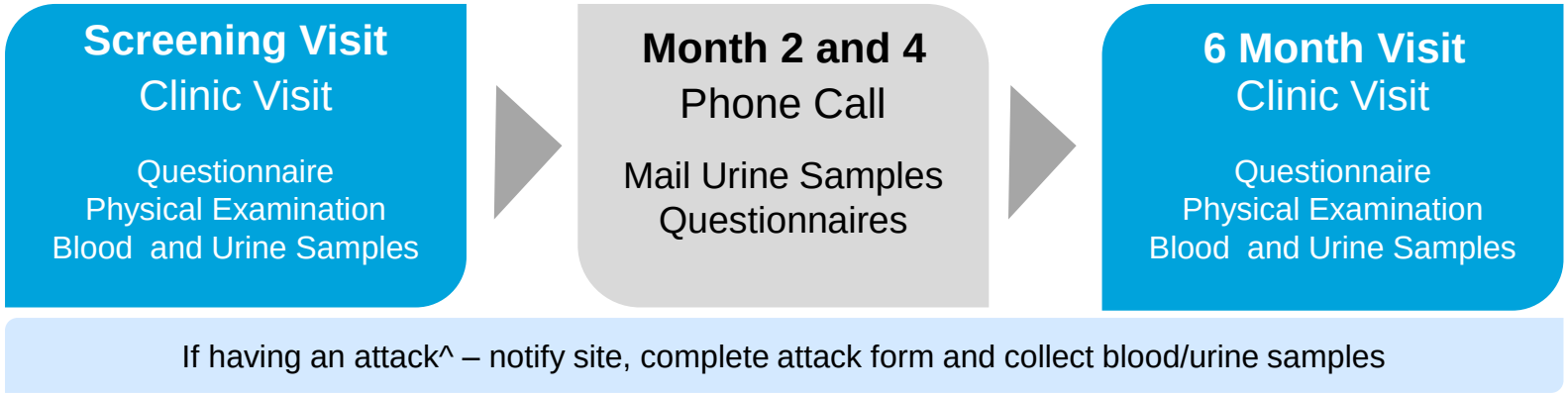
- Observational, multinational, prospective natural history study

Key Eligibility Criteria

- Males or Females ≥ 18 years old
- Diagnosis of acute hepatic porphyria (AHP) by specialist, including acute intermittent porphyria (AIP), hereditary coproporphyria (HCP) and variegate porphyria (VP)
- Recurrent attacks
  - 3+ attacks* within 12 months of screening
  - Using heme or a GnRH analog prophylactically

Key Objectives

- Characterize natural history and current AHP management
  - Medical history and medication usage
  - Porphyria signs and symptoms
  - Biomarkers
  - Quality of life



^Attacks defined as acute porphyria symptoms requiring increase in treatment (heme, pain medications, carbohydrates) or hospitalization

ClinicalTrials.gov Identifier: NCT02240784

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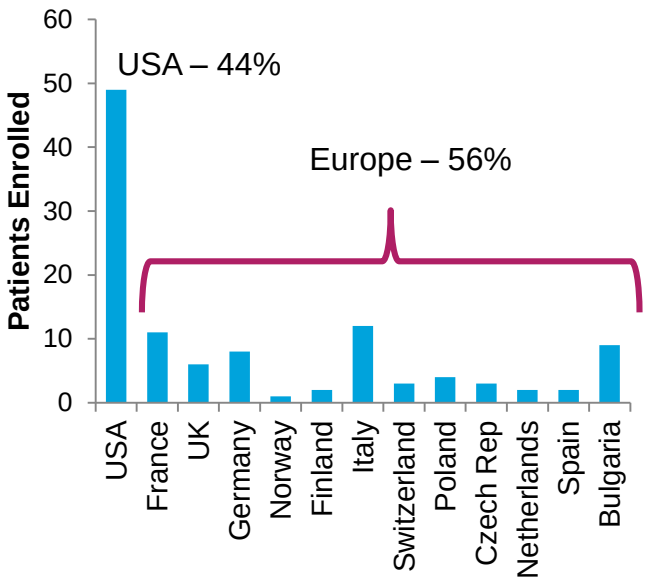
Enrollment and Demographics

Enrollment (N=112)



Demographics	Result
Age, mean	39 years
Sex, n (%)	
Female	100 (89)
Male	12 (11)
Race, n (%)	
White/Caucasian	95 (85)
Hispanic or Latino	5 (4)
Asian	3 (3)
Black/African American	3 (3)
Not Answered	11 (10)

AHP Disease Characteristics	Number Affected (%)
AIP	104 (93)
VP	5 (4)
HCP	3 (3)
Genotypes Represented	
AIP	63 (most common p.W283X [n=6])
VP	5
HCP	3

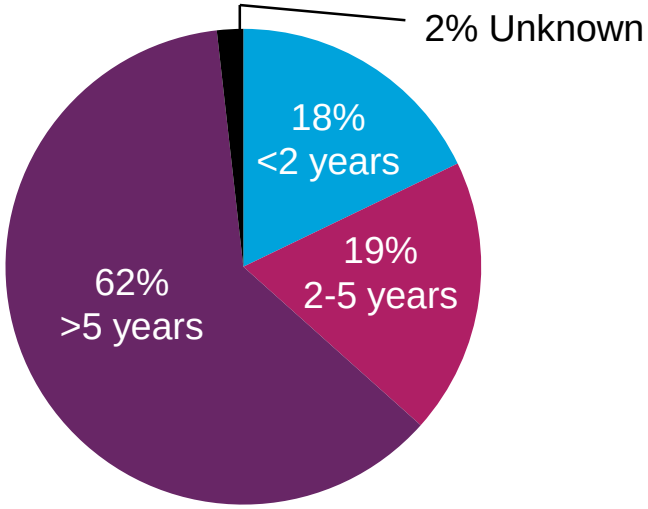
Associated Medical Conditions Most Common	Number Affected Total N=112, (%)
Gastrointestinal disorders	22 (20)
Nervous System disorders	33 (30)
Psychiatric/Sleep disorders	33 (30)
Renal and Urinary disorders	14 (12)
Vascular disorders	29 (26)

Data as of 17 AUG 2016

Baseline Data on Diagnosis and Porphyria Manifestations

Patient Self-Assessment Questionnaire

Years Since Diagnosis



Patient Reported Attack Data	Mean (median; range)
Number in last 12 months	9.5 (6; 0-54)

Patient Reported Symptoms/Treatment	Number (%)
Known attack triggers	98 (88)
Prodromal attack symptoms	98 (88)
Porphyria symptoms between attacks	72 (64)

Heme Use	Result (%)
Ever taken heme prophylaxis	61 (54)
Current heme prophylaxis	42 (38) (EU: 29% US:49%)
Mean time on heme prophylaxis	6.3 years
Change in prophylaxis frequency	45 (40) (Increased: 21%; Decreased: 13%; Stopped: 5%; Other: 1%)
Heme side effects	55 (49)

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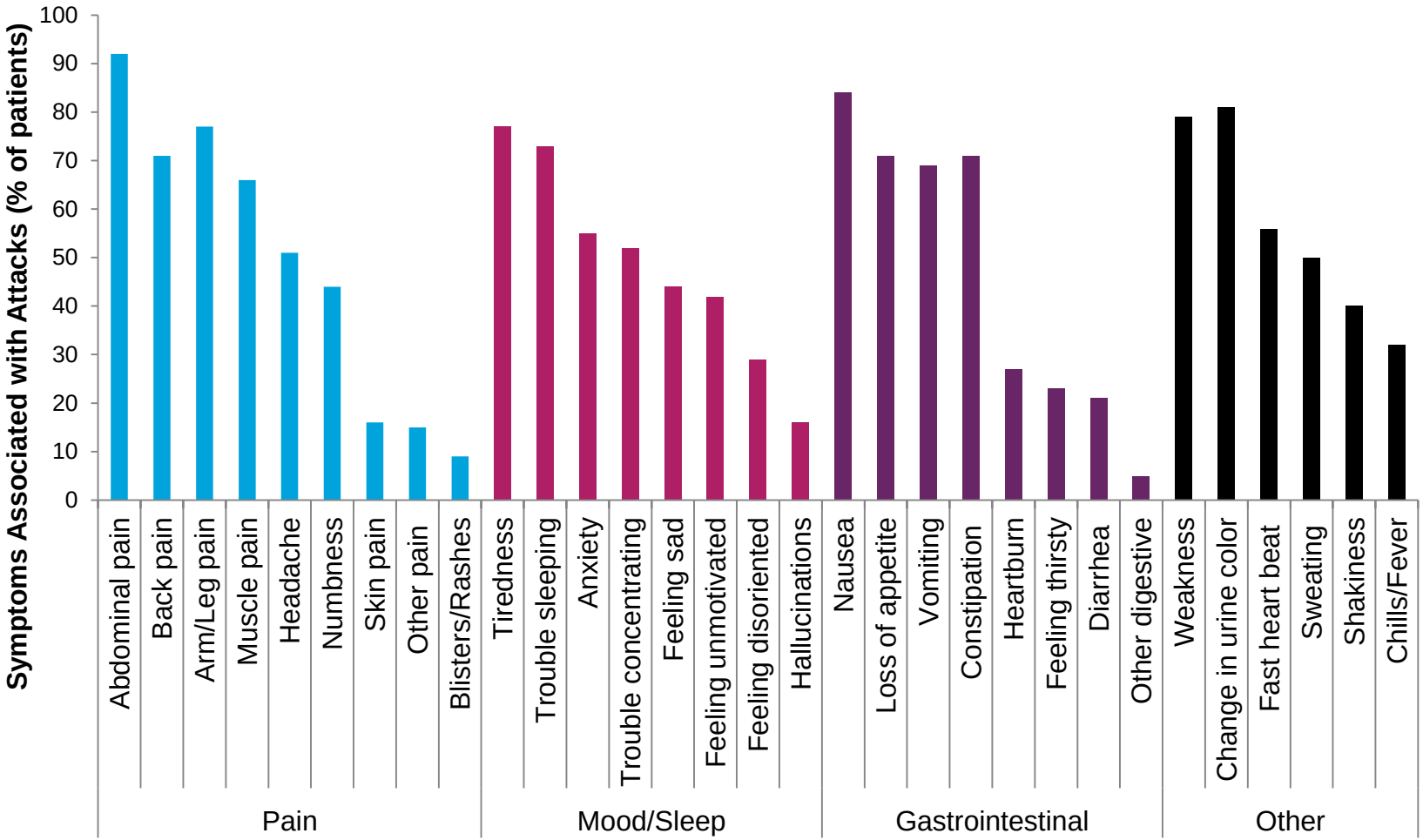
Patient-reported Attack Symptoms

Screening Questionnaire

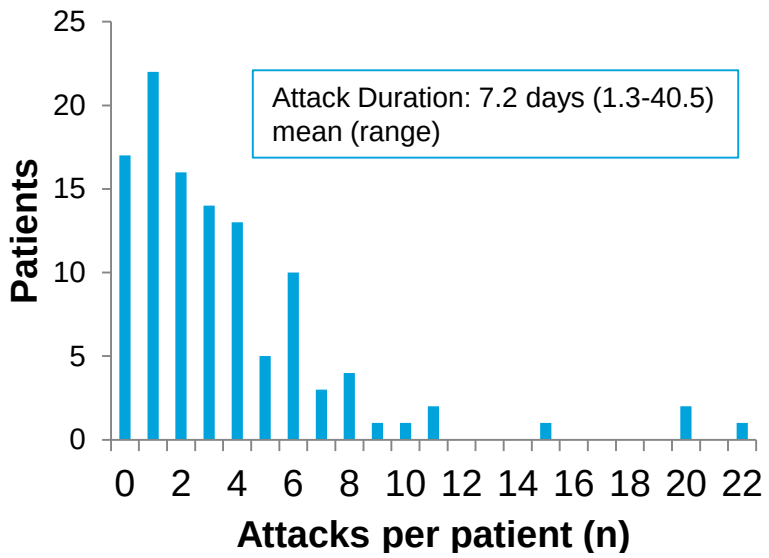


- Pain is a symptom found in 100% of attacks
- 46% of patients experience porphyria symptoms daily between attacks, most commonly pain (63%), weakness (20%), and nausea (20%)

Data as of 17 AUG 2016

On Study Attack Number and Treatment

95 patients experienced 404 attacks*



*101 patients completed 6 months of follow-up; 34 completed 12 months

	Current Heme Prophylaxis	
	No (n=70)	Yes (n=42)
Attacks on study	296	108
Annualized attack rate	5.5 attacks/ person	3.2 attacks/ person

Treatment Location

	% Attacks		
Location	Total	EU	US
Home	32%	36%	26%
Healthcare facility	68%	64%	73%
Unknown	0.2%	0%	0.6%

Treatment Type

	% Attacks		
Treatment	Total	EU	US
Included heme	66%	62%	72%
Included narcotics	50%	51%	49%
Included carbohydrates, NSAIDs, or other	38%	39%	38%
Treatment with heme or at a healthcare facility	76%	75%	78%

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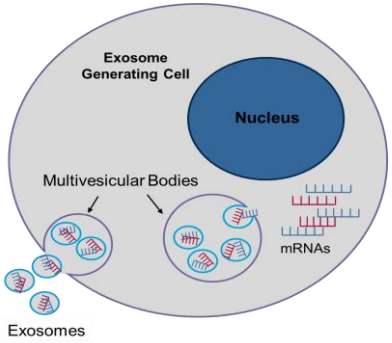
Porphyria Disease Biomarkers

Paired Urinary ALA/PBG Samples

Biomarkers	N	Asymptomatic Mean (range)	Attack Maximum Mean (range)	Attack Maximum Fold Above Asymptomatic (range)
PBG (mmol/mol Cr)	62	30.6 (0.5-111.2)	56.6 (0.3-843.9)	3.5 (0.1-32)
ALA (mmol/mol Cr)	59	29.6 (1.7-109.6)	66.8 (2.2-1016.6)	3.6 (0.4-39)

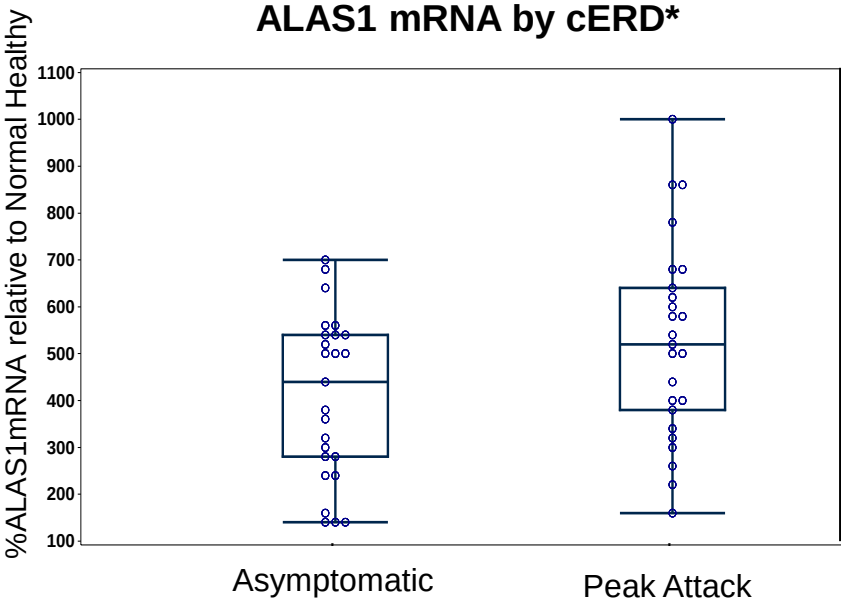
Upper Limit of Normal: PBG < 1.2 mmol/mol Cr; ALA < 3.1 mmol/mol Cr)

Liver ALAS1 mRNA via Circulating Extracellular RNA Detection (cERD)



- Exosomes that shed into bodily fluids from different cells contain mRNA derived from the tissue of origin
- Correlation of liver and serum ALAS1 mRNA shown in preclinical studies[1]
- Exosomes may be able to follow porphyria disease activity by monitoring ALAS1 mRNA in serum/urine without a liver biopsy

ALAS1 mRNA by cERD*

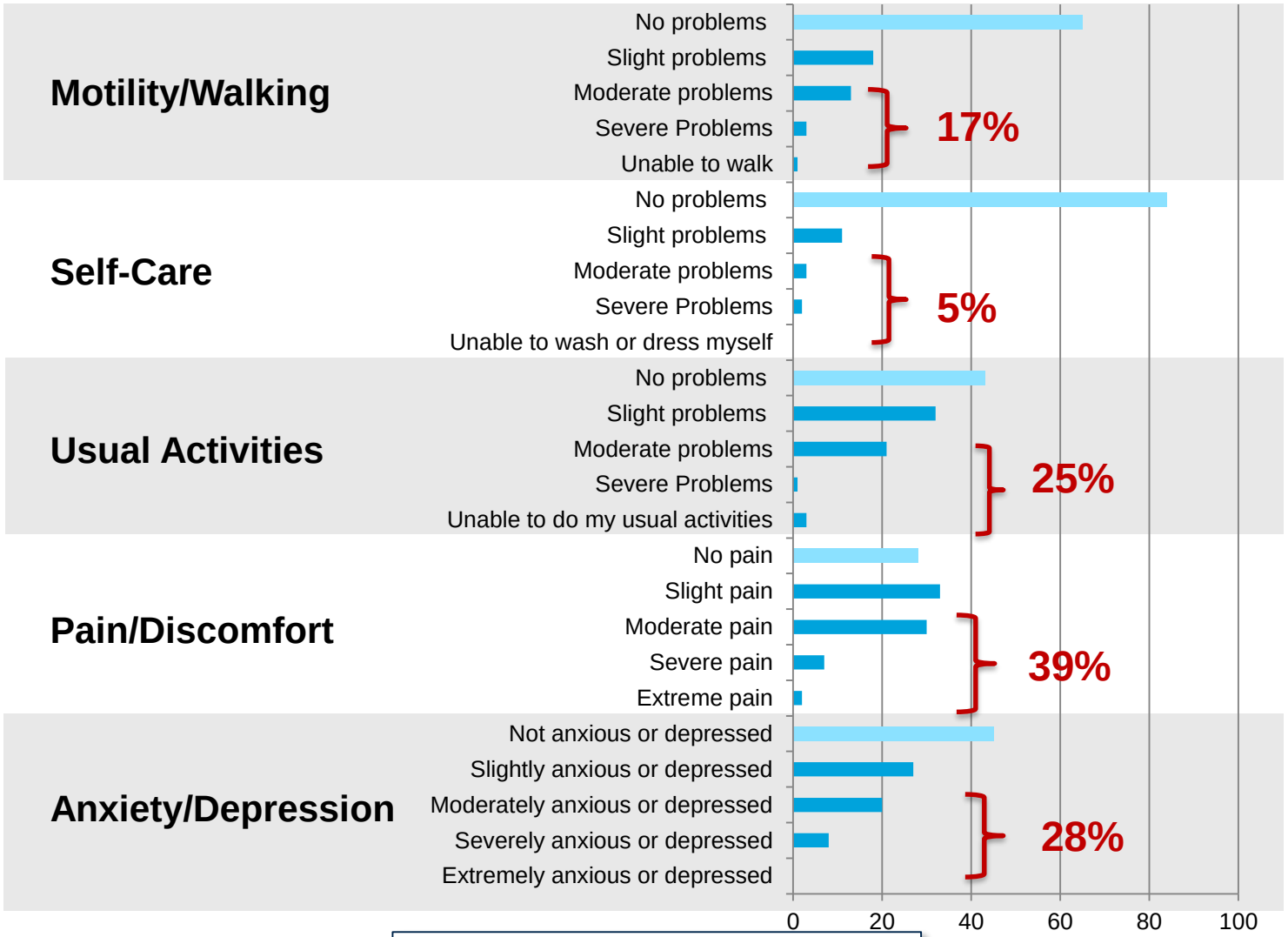


*paired urinary samples

[1]Chan A, et al. *Mol Ther Nucleic Acids*. 2015;4:e263.

Data as of 17 AUG 2016

Quality of Life: EQ-5D-5L at 6 Months (Asymptomatic)



N=100

Moderate or Greater Problems Reported

EQ-5D-5L Mean Summary Index = 0.78

- **0.79 in patients with diabetes mellitus[1]**
- **0.78 in patients with heart disease[2]**
- **0.82 in patients with hereditary angioedema[3]**

Data as of 17 AUG 2016

[1]Lin FJ, et al. *BMC Med Res Methodol*. 2014;14:78. [2]Nordenfelt P, et al. *Allergy Asthma Proc*. 2014;35(2):185-90.
[3]Lubetkin EI, et al. *Qual Life Res*. 2005;14(10):2187-96.

Porphyria-Related Reported Healthcare Utilization

Current Function in Past Year	%	Comments
Live at home with no special care	50%	Handling most personal needs (25%), need assistance (21%), bed bound (3%)
Currently working full-time	30%	27% on disability or unemployed
Had any missed days of work?	85%	Median days missed in last year: 20

Porphyria-Related Healthcare Usage in Past Year		
	Monthly or More Frequent (%)	**Every 2-12 Months (%)**
General practitioner visits	27 (24)	40 (36)
Specialist visits	40 (36)	60 (54)
ER visits	Mean: 2.8 (Range 0-20)	
Overnight hospitalizations	Mean 4.6 (Range 0-70)	
Duration of hospital stay (Days)	Mean: 6.6 (Range 1-60)	

Data as of 17 AUG 2016

EXPLORE Study Summary

AHP Disease Findings and Unmet Need

Baseline Demographics and Disease Characteristics

- Patients reported 9.5 attacks in the prior year, with pain as a cardinal feature in 100% of attacks
- Approximately 65% of patients experience porphyria symptoms between attacks, with almost 50% experiencing symptoms daily (most commonly pain)
- Patients report diminished quality of life and significant healthcare utilization

Biomarkers

- Non-invasive cERD assay enables monitoring of disease activity via changes in circulating ALAS1 mRNA
- Asymptomatic patients have induced ALAS1 and high ALA/PBG compared to normal healthy individuals, that increase further during attacks

Disease Activity and Management on Study

- Annualized attack rate on study of 4.4 attacks per person with mean duration of 7 days
  - 5.5 attacks/person if treated on demand; 3.2 attacks/person if on heme prophylaxis
  - Lower attack rate on study may relate to underreporting by patients of home attacks
- Approximately 76% of attacks required treatment with heme or at a healthcare facility
- Novel therapies are needed to prevent acute attacks and decrease chronic symptoms

Next Steps

- EXPLORE study is ongoing and patients will be followed for a total of 12 months with an extension study planned in 2017

References

[1]Bonkovsky HL, et al. *Am J Med*. 2014;127(12):1233-41.
[2]Elder G, et al. *J Inherit Metab Dis*. 2013;36(5):849-57.
[3]Chan A, et al. *Mol Ther Nucleic Acids*. 2015;4:e263.
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[5]Nordenfelt P, et al. *Allergy Asthma Proc*. 2014;35(2):185-90.
[6]Lubetkin EI, et al. *Qual Life Res*. 2005;14(10):2187-96.

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