



# EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyrias (AHP) with Recurrent Attacks

Colin  
*Living with Porphyria*

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# EXPLORE Natural History Study

## Study Design Overview



### Study Design

- Observational, multinational, prospective on-going natural history study

### Key Eligibility Criteria

- Males or Females  $\geq 18$  years old
- Diagnosis of AHP by specialist, including acute intermittent porphyria (AIP), hereditary coproporphyrinuria (HCP) and variegate porphyria (VP)
- Recurrent attacks
  - 3+ attacks<sup>^</sup> within 12 months of screening
  - Using hemin or 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 (QoL)

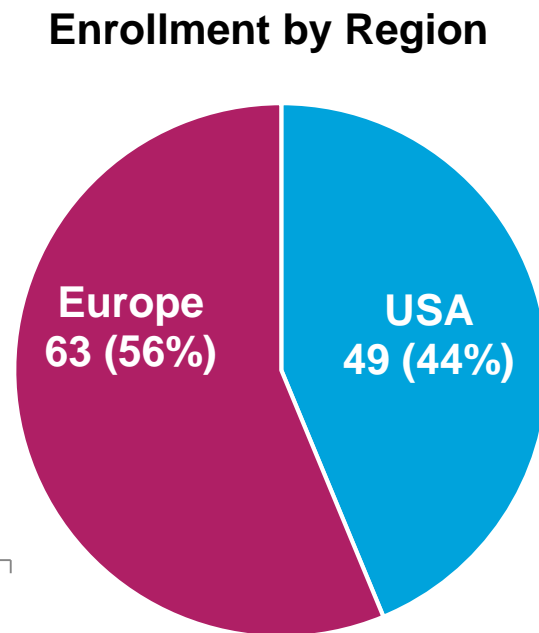
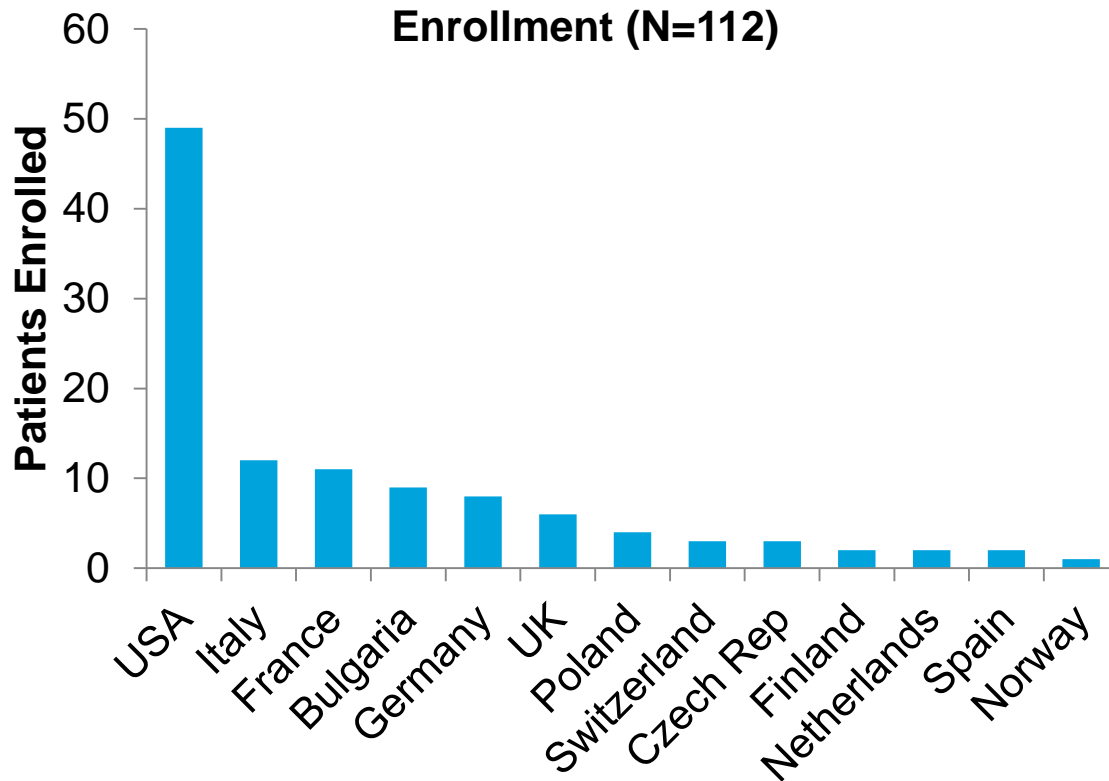


If having an attack<sup>^</sup> – notify site, complete attack form and collect blood/urine samples

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

# EXPLORE Natural History Study

## 12-Month Study Enrollment and Follow-Up



Follow-Up Time, n (%)	N=112
≥6 months	107 (96%)
≥12 months	80 (71%)

# EXPLORE Natural History Study

## Demographic and Baseline Clinical Characteristics

### Demographics

**N=112**

Mean Age, years

39.3

#### 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%)

### Disease Characteristics

#### AHP etiology: AHP type

**n (%)**

AIP

104 (93%)

VP

5 (4%)

HCP

3 (3%)

#### Genotypes represented

**n**

AIP<sup>†</sup>

56

VP / HCP

7

### Most Common Associated Medical Conditions

**n (%)**

#### Renal/Vascular Disorders

**43 (38%)**

Hypertension

26 (23%)

Chronic Kidney Disease

9 (8%)

#### Nervous System Disorders

**35 (31%)**

Headaches/Migraine

12 (11%)

Neuropathy/Nerve Pain

10 (9%)

#### Psychiatric/Sleep Disorders

**33 (30%)**

Depression

19 (17%)

Insomnia

13 (12%)

Anxiety

9 (8%)

#### Gastrointestinal Disorders

**25 (22%)**

GERD

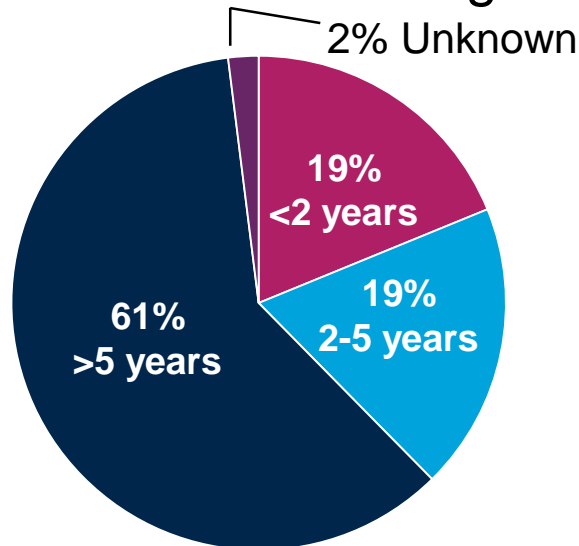
9 (8%)

# EXPLORE Natural History Study

## Baseline Diagnosis and Porphyria Manifestations

### Patient Self-Assessment Questionnaire

#### Years Since Diagnosis



#### Patient-Reported Symptoms/Treatment

N (%)

Known attack triggers	98 (88%)
Prodromal attack symptoms	98 (88%)

#### Patient-Reported Attack

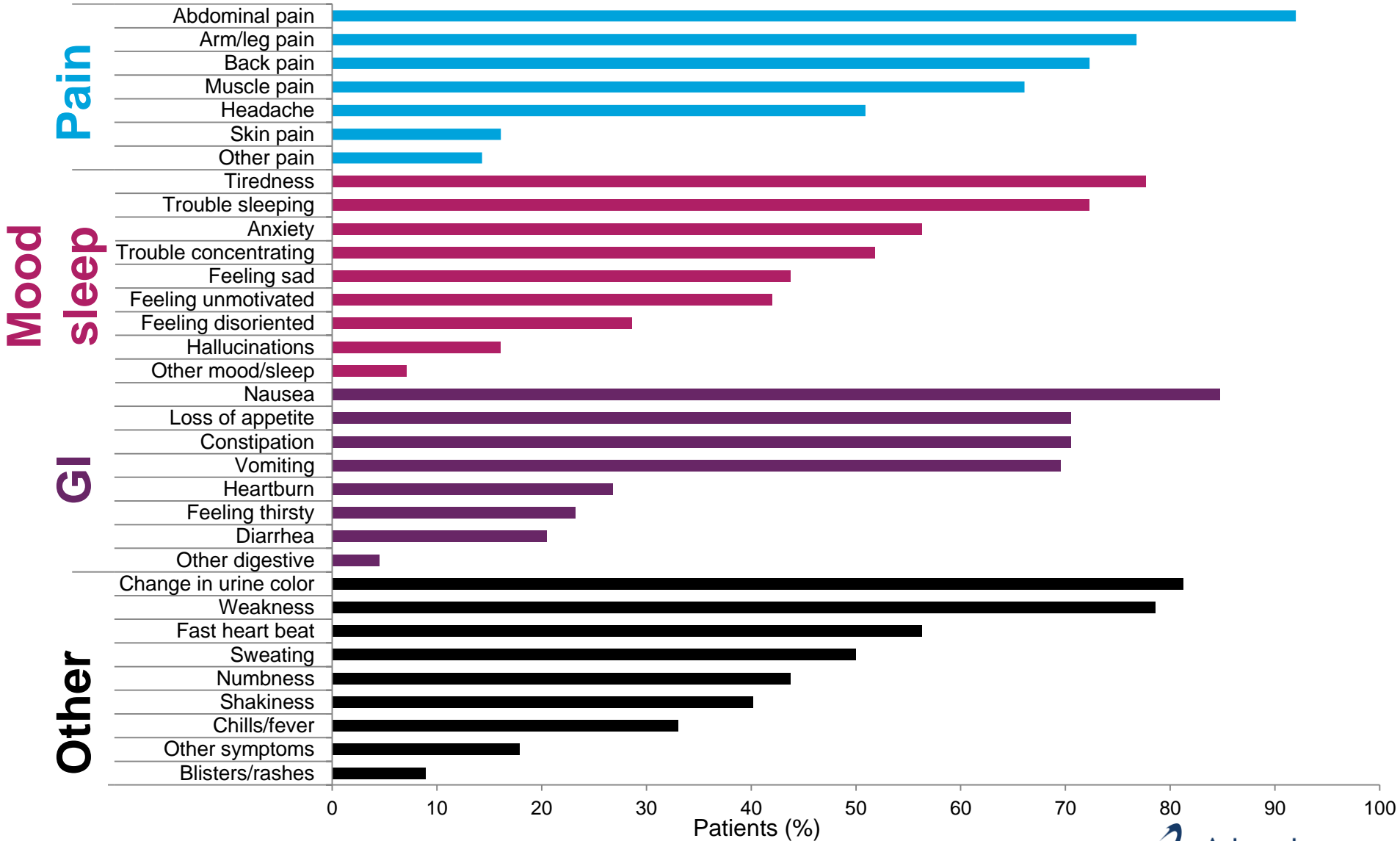
Number of attacks in last 12 months	
Mean (SD)	9.3
Median (range)	6 (0, 54)

#### Hemin Use

Ever taken hemin prophylaxis, n (%)	61 (54%)
Current hemin prophylaxis, n (%)	52 (46%)
Frequency regular basis hemin use, n (%)	
Weekly	27 (24%)
Monthly	13 (12%)
Other	20 (18%)
Time on hemin prophylaxis, years	n=48
Mean (SD)	7.3 (7.0)
Change in prophylaxis frequency, n (%)	45 (40%)
More frequent	23 (21%)
Less frequent	15 (13%)
Stopped	6 (5%)
Other	1 (1%)
Hemin side effects, n (%)	55 (49%)

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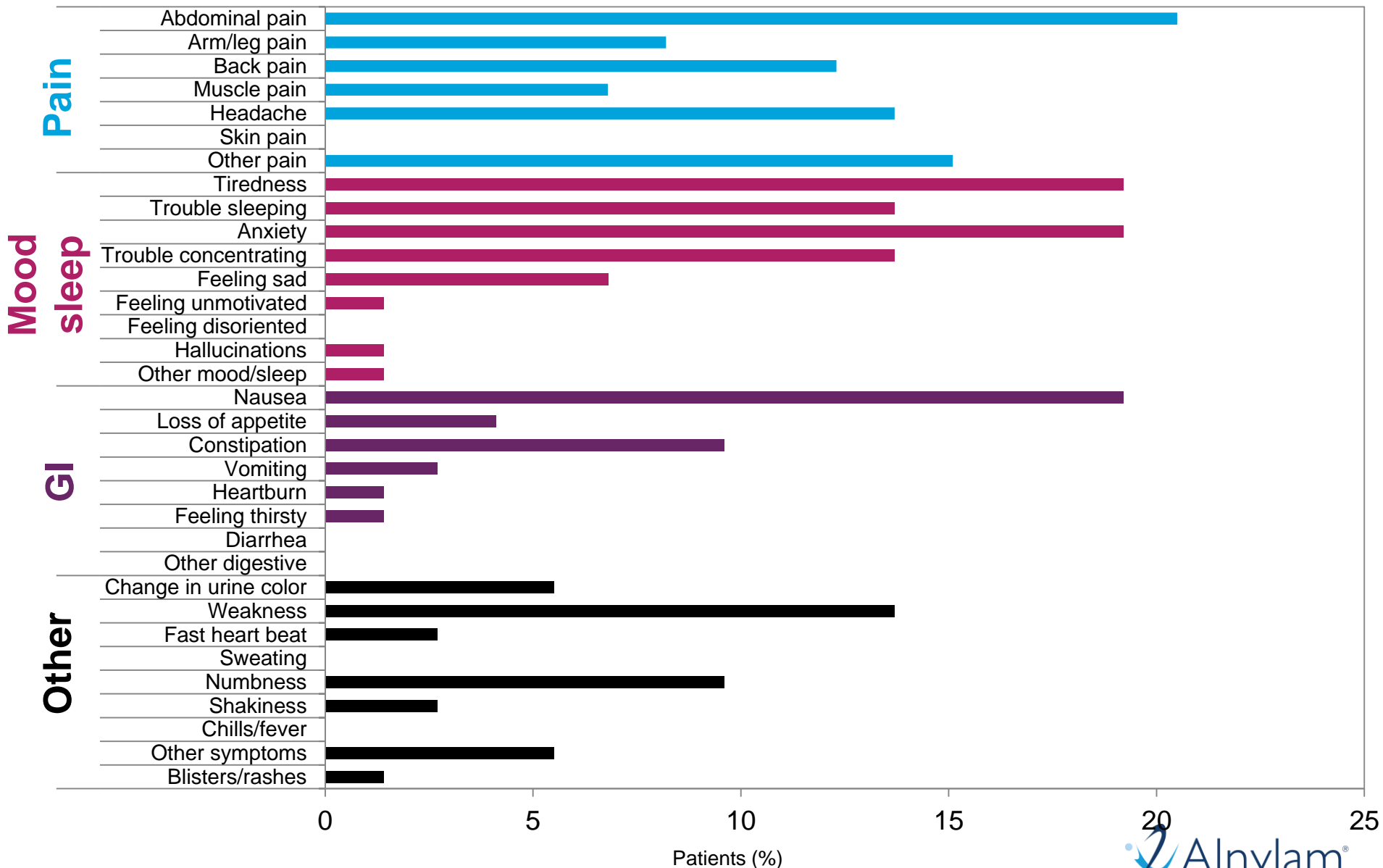
## Screening Questionnaire: Patient-Reported Attack Symptoms



Symptoms in  $\geq 80\%$ : abdominal pain; nausea; change in urine color

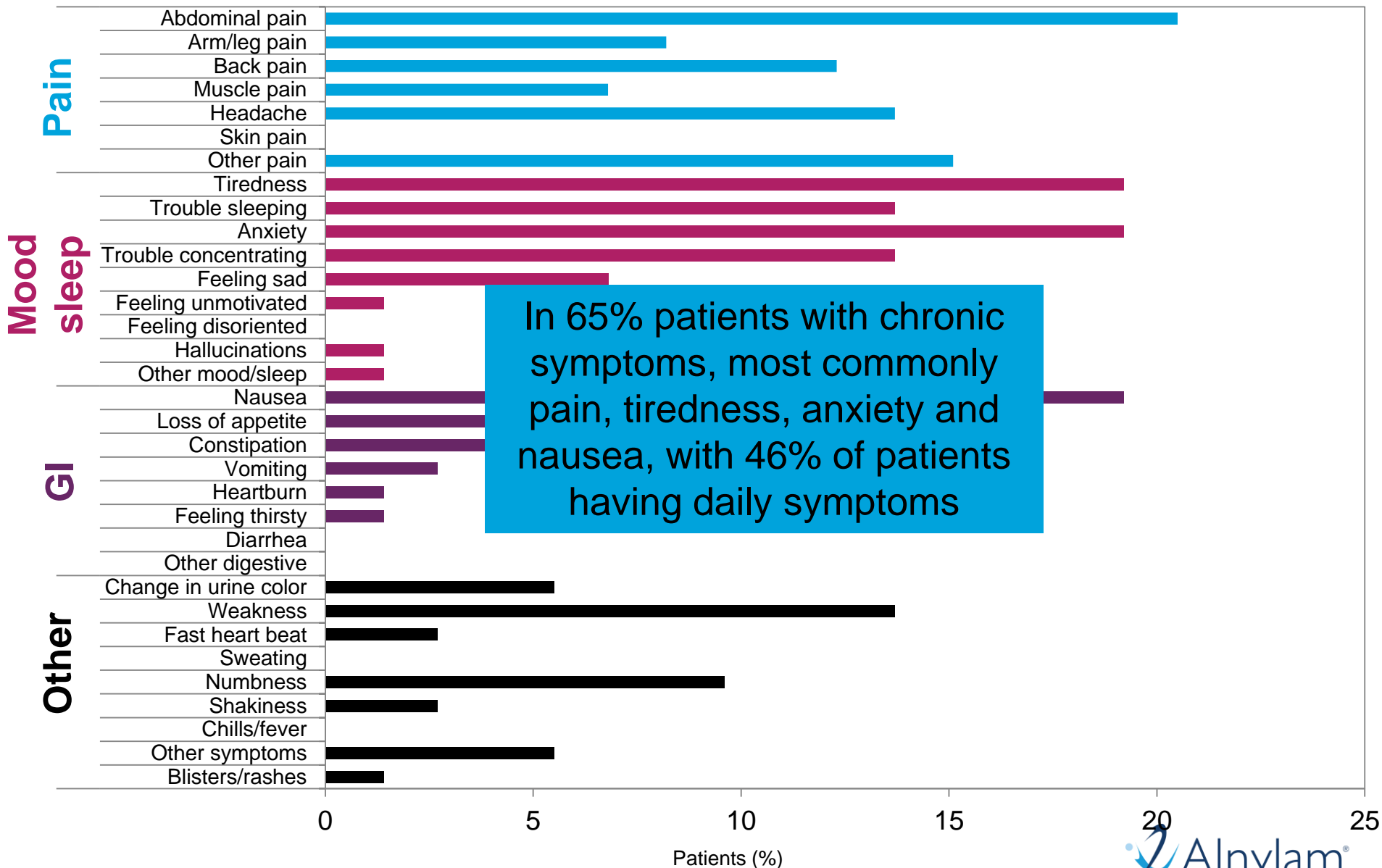
# EXPLORE Natural History Study

## Screening Questionnaire: Patient-Reported Chronic Symptoms



# EXPLORE Natural History Study

## Screening Questionnaire: Patient-Reported Chronic Symptoms





# EXPLORE Natural History Study

## Attacks During Study

**96 patients experienced 481 attacks\***

### Attack characteristics (N=94)

Mean (range) attack duration, days 7.05 (1.3–33.2)

### Attack rate per person-year

Overall 4.9

#### Chronic symptoms

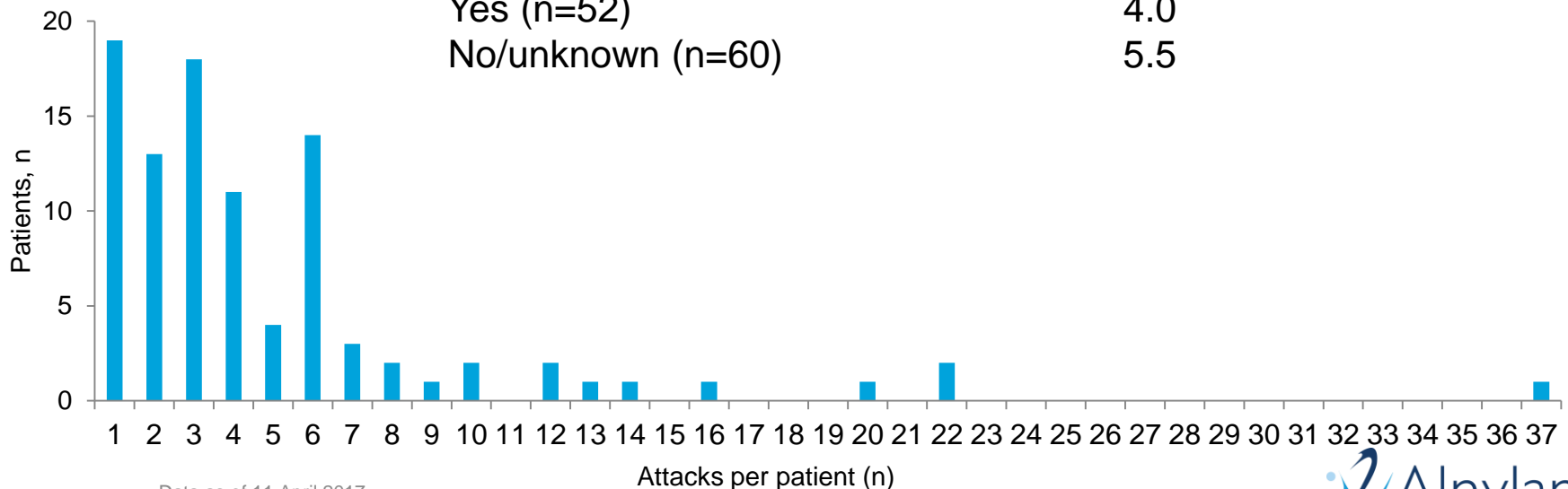
Yes (n=52) 5.1

No (n=57) 4.8

#### Current hemin prophylaxis

Yes (n=52) 4.0

No/unknown (n=60) 5.5



Data as of 11 April 2017

\*In patients completing 12 months of follow up.

# EXPLORE Natural History Study

## Attack Treatment During Study Follow-Up

Attack Treatment	% of Attacks		
	Total	EU	US
<b>Treatment location</b>			
Home	31%	33%	27%
Healthcare facility	69%	68%	72%
Unknown	0.2%	0%	0.6%
<b>Treatment type</b>			
Included hemin	69%	68%	71%
Included narcotics	55%	58%	50%
Included carbohydrates, NSAIDs*, or other	45%	44%	46%
Treatment with hemin or at healthcare facility	77%	76%	77%

Data as of 11 April 2017

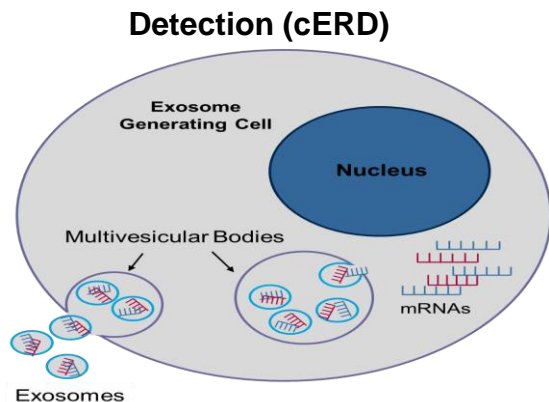
\*Non-steroidal Anti-inflammatory drugs.

# EXPLORE Natural History Study Disease Biomarkers

## Paired Urinary ALA/PBG Samples

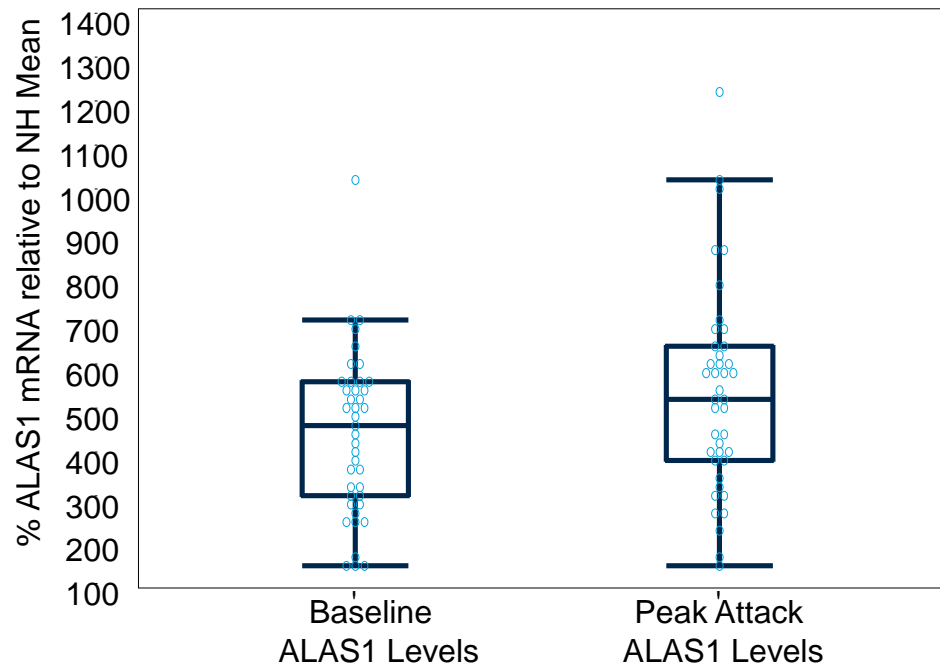
Biomarkers <sup>†</sup> (N=65 ALA, N=66 PBG)	Non-Attack Mean (range)	Attack Maximum Mean (range)	Attack Maximum Fold Above Non-Attack
PBG (mmol/mol Cr)	31.2 (0.5-87.3)	57.6 (0.3-843.9)	3.5 (0.1-31.9)
ALA (mmol/mol Cr)	29.8 (1.7-109.6)	64.1 (2.2-1019.6)	3.4 (0.4-39.0)

### Liver ALAS1 mRNA via Circulating Extracellular RNA



- Exosomes shed into bodily fluids from different cells contain mRNA derived from non-human tissue of origin
- Correlation of liver and serum ALAS1 mRNA shown in preclinical studies<sup>1</sup>
- Exosomes may enable monitoring of porphyria disease activity through changes in circulating ALAS1 mRNA in urine/serum

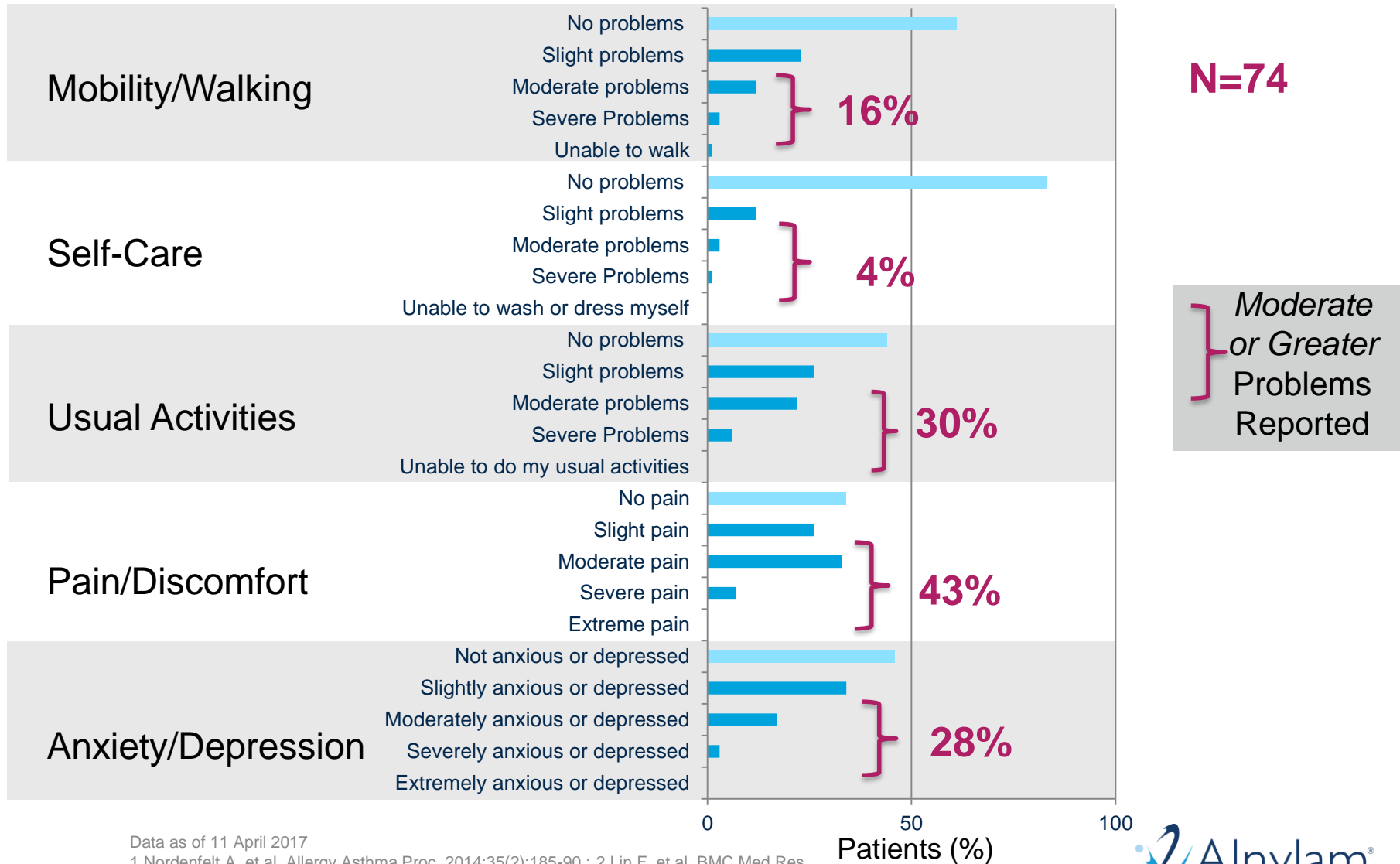
### Urinary ALAS1 mRNA by cERD \*



\*Normal Healthy (NH) derived from healthy individuals not in study

# EXPLORE Natural History Study

## Quality of Life: EQ-5D-5L at 12 Months (Non-attack)

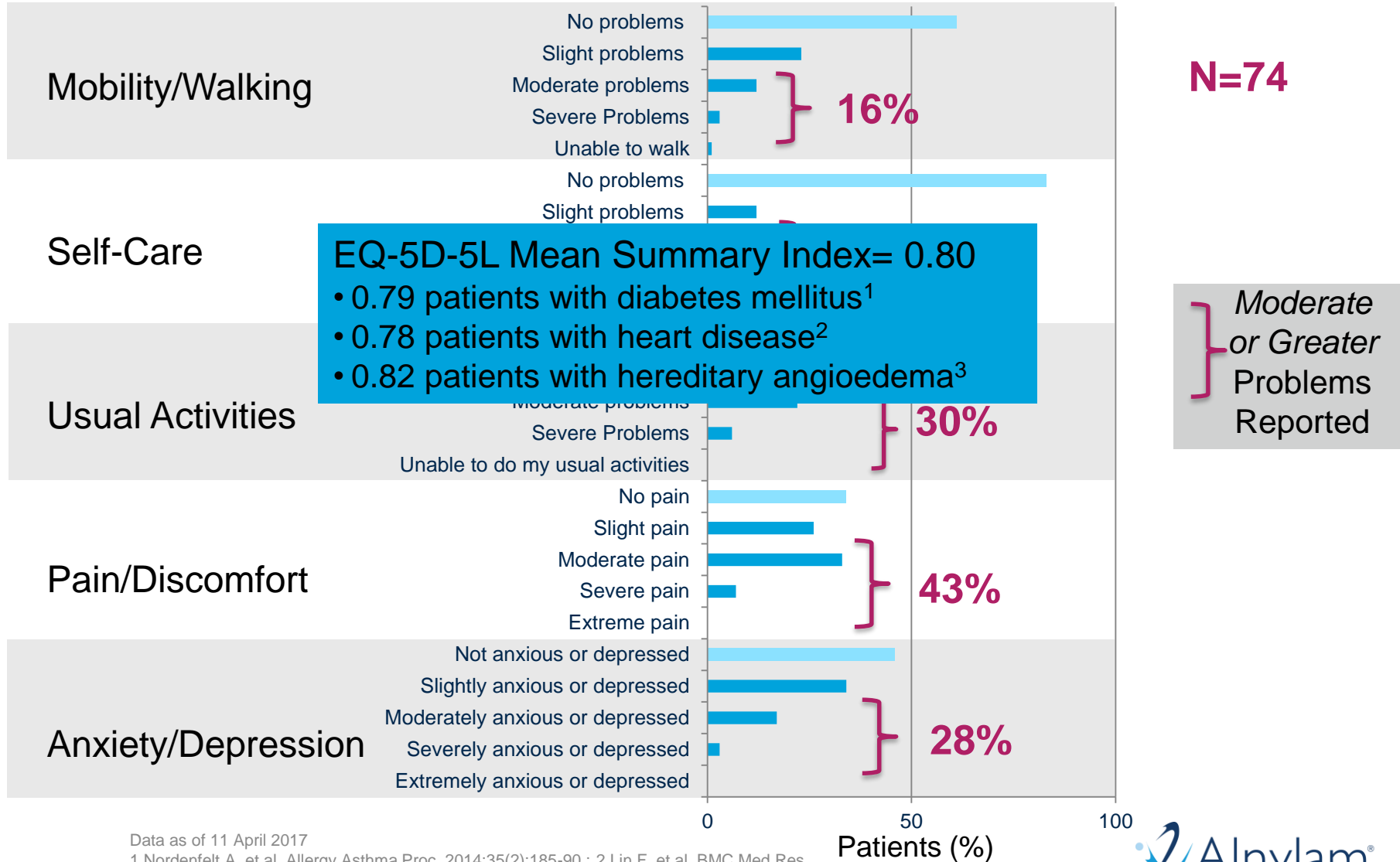


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1. Nordenfelt A, et al. Allergy Asthma Proc. 2014;35(2):185-90.; 2. Lin F, et al. BMC Med Res Method. 2014;14:78. 3. Lubetkin E, et al. Qual Life Res. 2005;14(10):2187-96.

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# EXPLORE Natural History

## Summary: AHP Disease Findings and Unmet Need

### Baseline Demographics and Disease Characteristics

- Patients had a mean of 9.3 attacks in prior year, with severe pain cardinal feature in 99% of attacks
- Approximately 65% of patients experience chronic porphyria symptoms (most commonly pain), with 46% overall experiencing symptoms daily

### 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 Study Management

- Annualized attack rate on study of 4.9 attacks/person with mean duration of 7 days
  - 5.5 attacks/person if not on hemin prophylactically; 4.0 attacks/person if on hemin prophylactically
  - Lower attack rate on study may relate to underreporting by patients of home attacks
- ~77% of attacks required treatment with hemin or at healthcare facility
- Patients report diminished QOL, most often in domains of pain, usual activities and anxiety/depression
- Novel therapies are needed to prevent attacks and decrease chronic symptoms

Please see posters PO15 and PO19 for further information on health care utilization and qualitative research on AHP from the patient perspective

# Acknowledgements

## EXPLORE Investigators and Contributors



- **Karl Anderson**
- **Herb Bonkovsky**
- **Montgomery Bissell**
- **John Phillips**
- **Charles Parker**
- **Manisha Balwani**
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- **Desiree Lyon**
- **Jessica Hungate**
- **Natalia Sturza**

### Mount Sinai

- **Hetanshi Naik**

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- Karl Anderson
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Mount Sinai