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

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14 April 2018 | The International Liver Congress | Paris, France

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Disease Overview

Acute Hepatic Porphyrias (AHPs)[1,2]

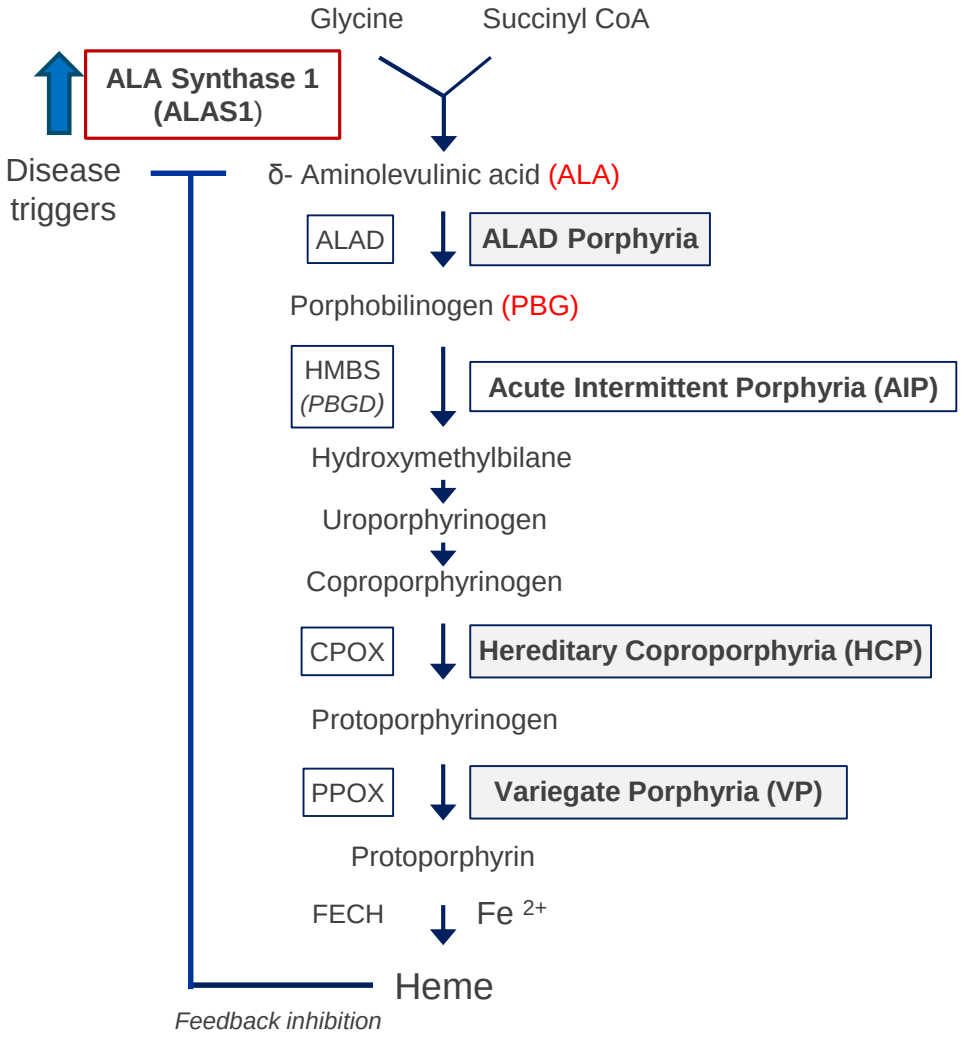
- Inborn errors of heme synthesis from liver enzyme defects
- Acute Intermittent Porphyria (AIP) most common, with mutation in hydroxymethylbilane synthase (HMBS)

Disease Pathophysiology

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

Attacks and Chronic Manifestations

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



1.Bonkovsky, et al. Am J Med. 2014;127(12):1233-41; 2. Elder, et al. JIMD. 2013;36(5):849-57.

EXPLORE Natural History Study
Study Design Overview

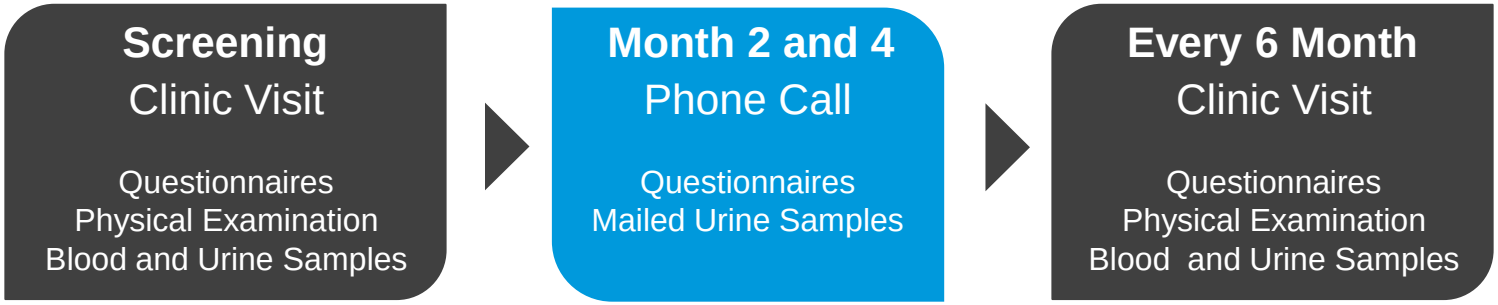
Study Design
- Observational, multinational, prospective natural history study

Key Eligibility Criteria
- Males or females ≥ 18 years old
- Diagnosis of AHP
  - Acute intermittent porphyria (AIP), hereditary coproporphyria (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
  - Porphyria signs and symptoms
  - Biomarkers
  - Quality of life (QoL)

Part B ongoing and enrolling patients
- Phone call every 3-6 months for 3 years with no clinic visits required

Part A Assessments

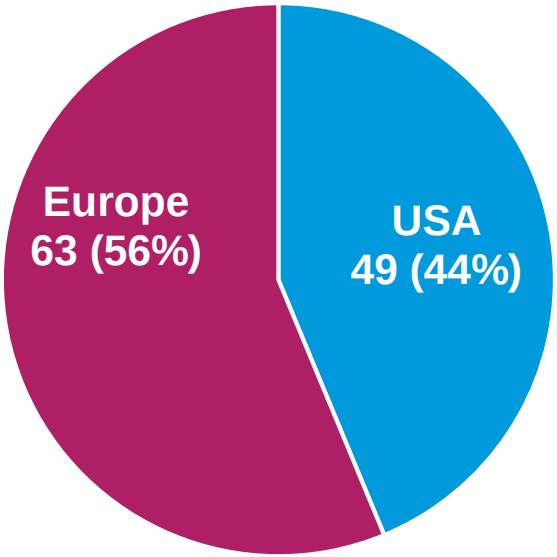


If having an attack^ – notify site, complete attack form and collect blood/urine samples

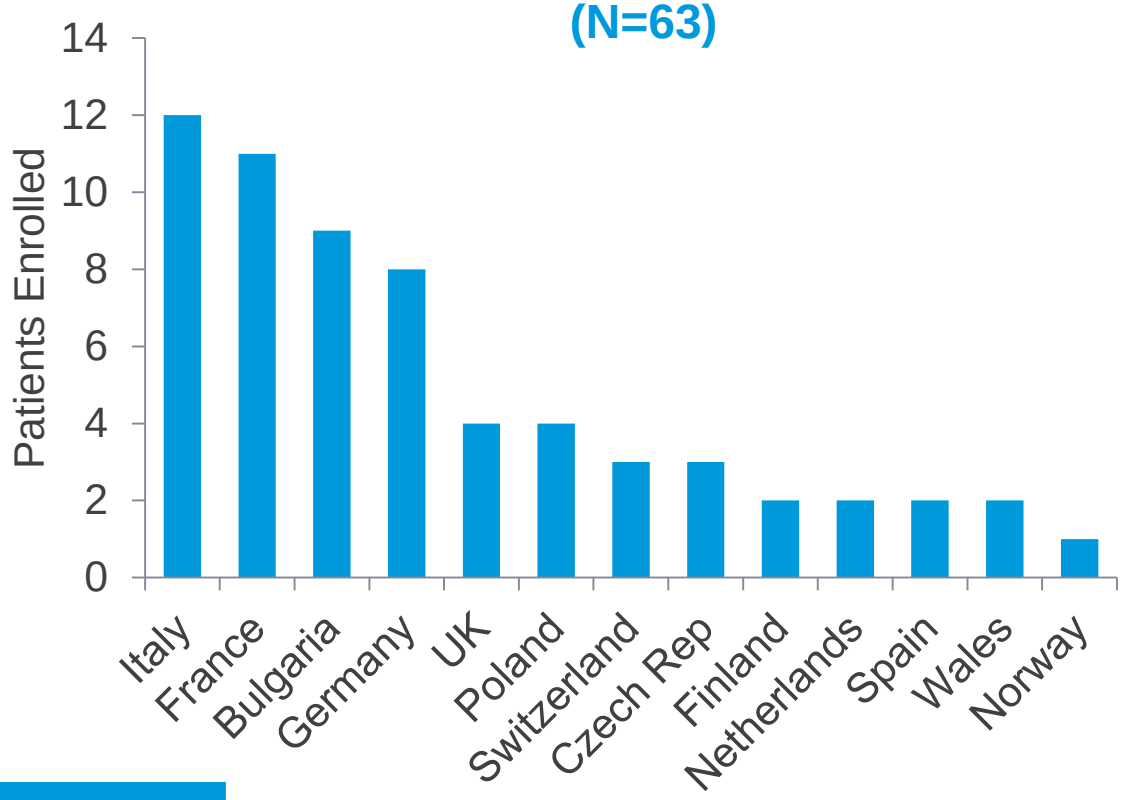
^Attacks defined as acute porphyria symptoms requiring increase in treatment (hemin, pain medications, carbohydrates) or hospitalization
ClinicalTrials.gov Identifier: NCT02240784; GnRH, Gonadotropin-releasing hormone

EXPLORE Natural History Study
Study Enrollment and Follow Up

Enrollment by Region (N=112)



Enrollment in Europe by Country (N=63)



Follow Up Time (months)	N=112
Mean (SD)	11 (3)
Median (Range)	12 (9-12)

Data as of 21 Nov 2017.

EXPLORE Natural History Study
Demographics and Baseline Clinical Characteristics

Demographics	N=112
Age, mean (range)	**39.3 (19-70)**
Sex	**N (%)**
Male	12 (11)
Female	100 (89)
Race	**N (%)**
White/Caucasian	95 (85)
Asian	3 (3)
Black/African American	3 (3)
Not Answered	11 (10)

Disease Characteristics	
AHP type	**N (%)**
AIP	104 (93)
VP	5 (4)
HCP	3 (3)
Genotypes represented	**N**
AIP[†]	58
VP / HCP	7

Most Common Associated Medical Conditions	N (%)
Vascular Disorders	**30 (27)**
Hypertension	27 (24)
Renal Disorders	**15 (13)**
Chronic Kidney Disease	3 (3)
Nervous System Disorders	**35 (31)**
Migraine	7 (6)
Headaches	5 (5)
Peripheral Neuropathy	7 (6)
Psychiatric/Sleep Disorders	**34 (30)**
Depression	20 (18)
Insomnia	13 (12)
Anxiety	9 (8)
Gastrointestinal Disorders	**25 (22)**
GERD	9 (8)
Nausea	4 (4)

Data as of 21 Nov 2017. GERD; Gastroesophageal reflux disease. AIP; Acute Intermittent Porphyria. VP; variegate porphyria. HCP; hereditary coproporphyria. AHP; Acute Hepatic Porphyria.[†]p.R173W and p.W283X were most common (n=4 each).

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EXPLORE Natural History Study
Baseline Porphyria Manifestations and Management

Patient Self-Assessment Questionnaire

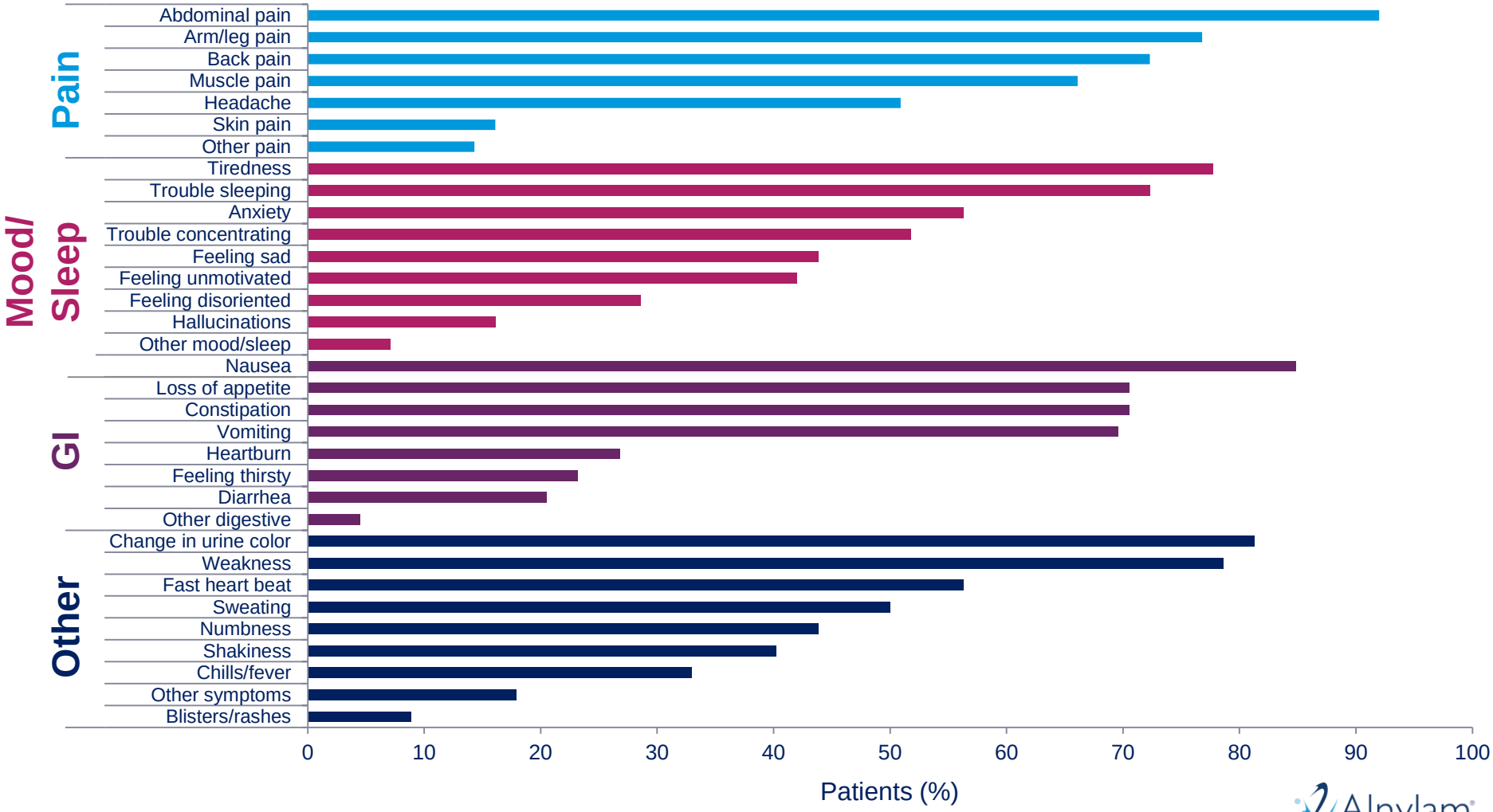
Patient-Reported Attacks	
Number of attacks in last 12 months	
Mean (SD)	9.3 (10.0)
Median (range)	6 (0–54)
Number of patients reporting number of attacks	**N (%)**
0 attacks	7 (6)
1 – 2 attacks	5 (5)
3 – 5 attacks	42 (38)
6 – 10 attacks	21 (19)
>10 attacks	36 (32)
Attack characteristics/symptoms	**N (%)**
Known attack triggers	98 (88)
Prodromal attack symptoms	98 (88)

Hemin Use	N (%)
Ever taken hemin for attacks	**94 (84)**
Usual frequency of hemin use per attack	
1 day	15 (13)
2–4 days	60 (54)
>4 days	19 (17)
Ever taken hemin prophylaxis	**61 (55)**
Frequency of hemin prophylaxis	
Weekly	27 (24)
Monthly	13 (12)
Other	20 (18)
Duration of hemin prophylaxis	
<1 year	15 (13)
1–2 years	8 (7)
>2 years	36 (32)
Side effects from hemin	**55 (49)**

Data as of 21 Nov 2017. SD; Standard Deviation

EXPLORE Natural History Study
Baseline Patient-Reported Attack Symptoms

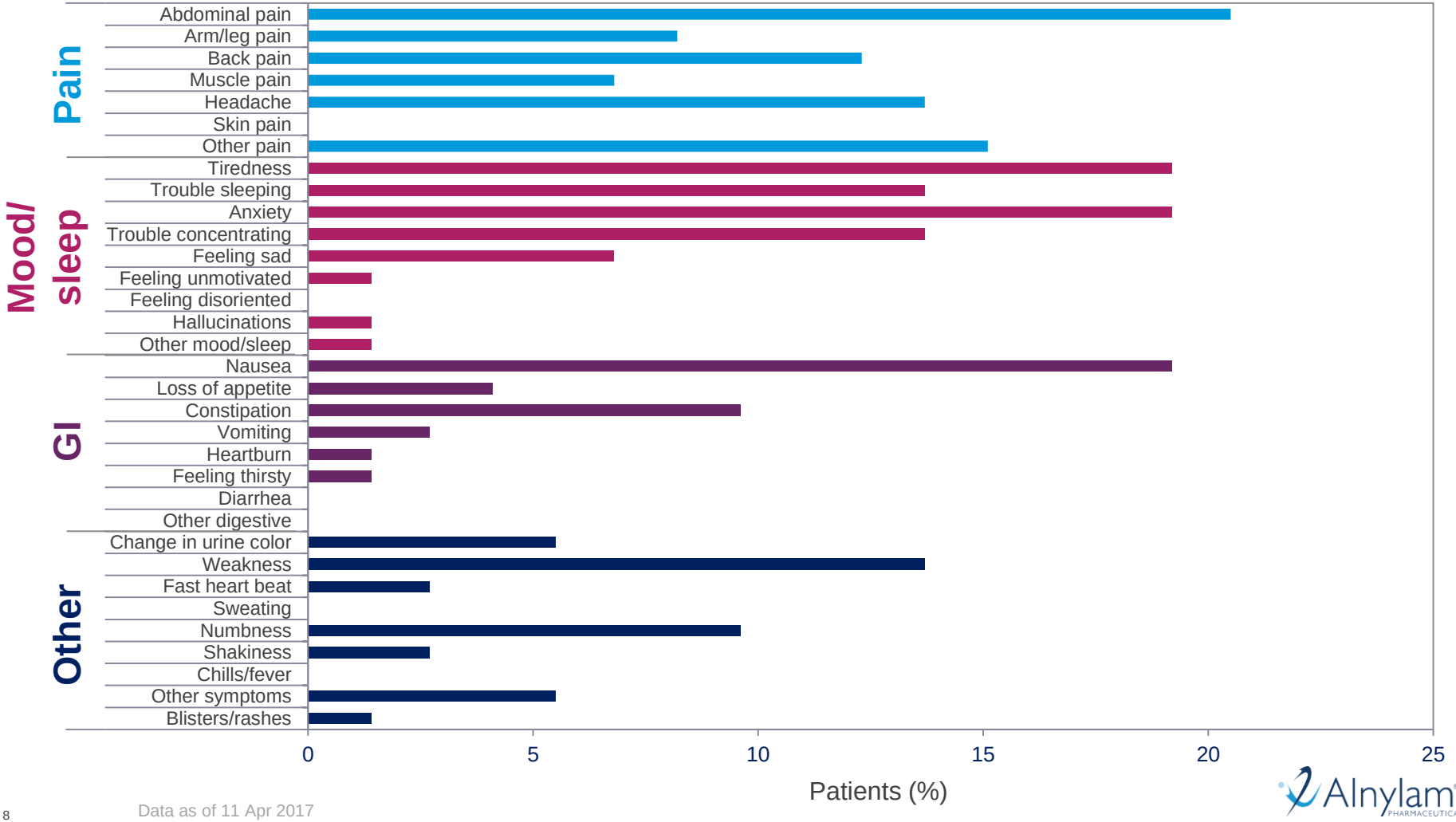
- Symptoms reported by > 80% of patients: abdominal pain, nausea, change in urine color



Data as of 11 April 2017

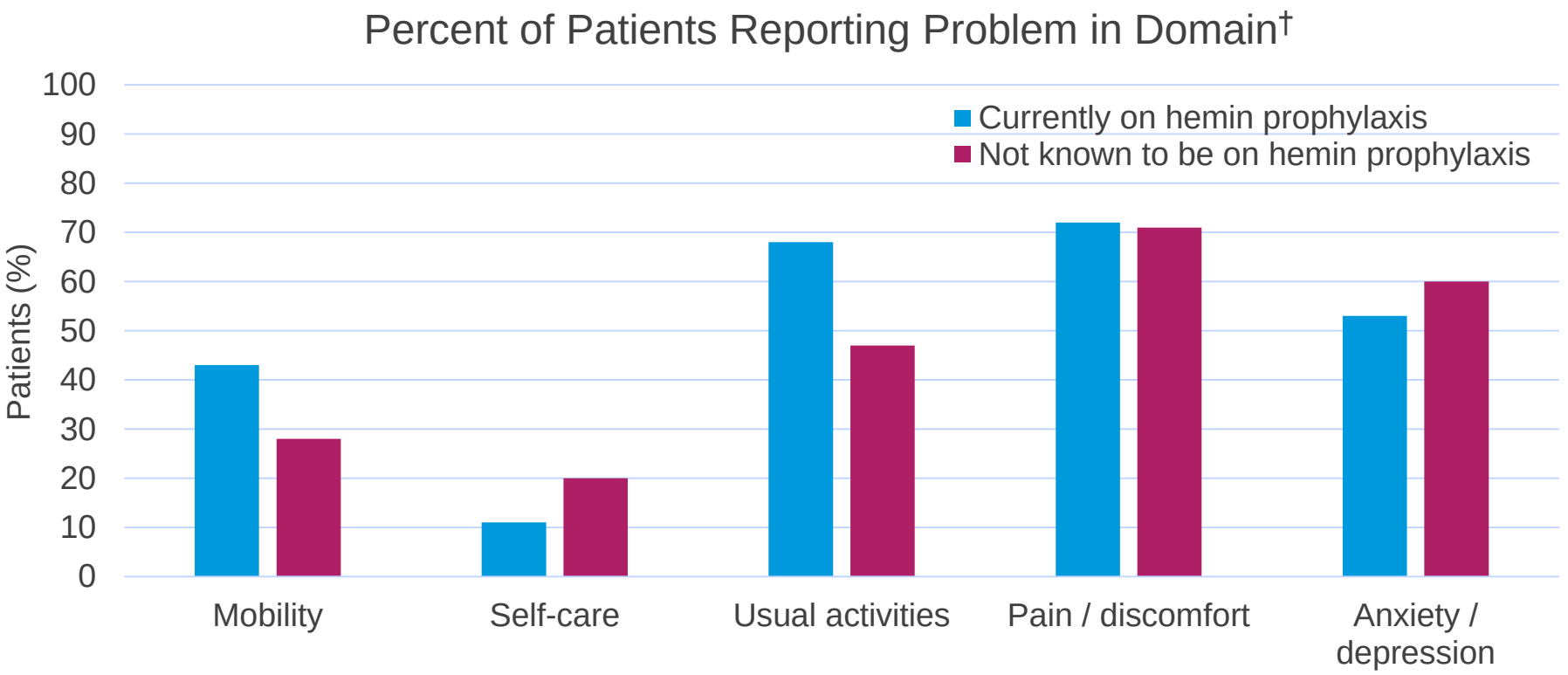
EXPLORE Natural History Study
Baseline Patient-Reported Chronic Symptoms

- 65% patients with chronic symptoms, most commonly pain, tiredness, anxiety and nausea, with 46% reporting daily symptoms



Data as of 11 Apr 2017

EXPLORE Natural History Study
Baseline QoL Using EQ-5D-5L Domains



- Health status domains of usual activities, pain/discomfort and anxiety/depression are most impacted
- Domains not impacted by hemin prophylaxis treatment status

Data as of 11 Apr 2017

†includes patients reporting a problem level ≥2, on a scale from 1-5 (1=no, 2=slight, 3=moderate, 4=severe, 5=extreme); hemin prophylaxis status at time of enrollment

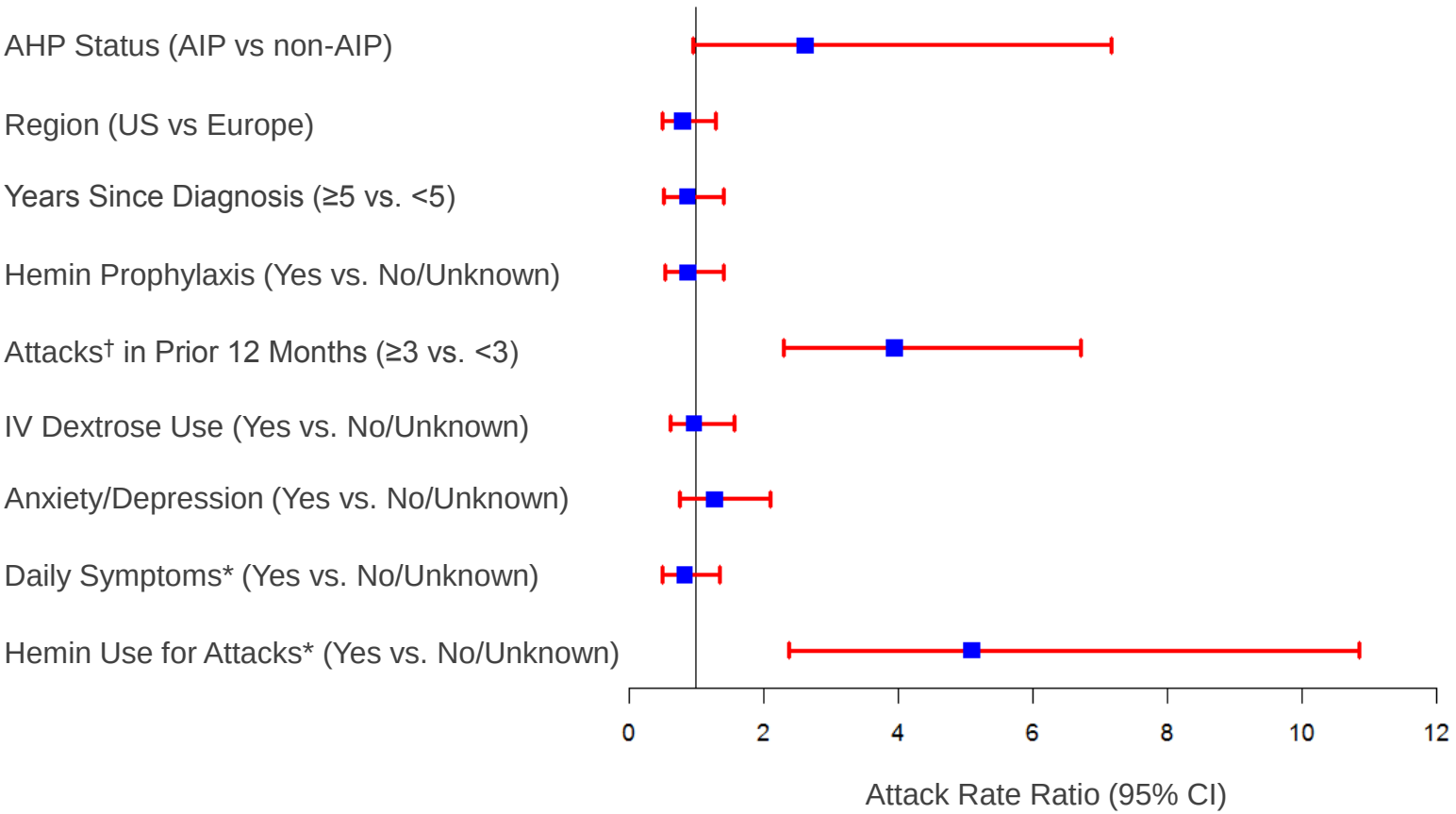
EXPLORE Natural History Study
Attacks on Study

97 patients experienced 483 attacks

Attack Characteristics	N (%)
Attack duration, days, mean (range)	**7.3 (1–51)**
Attack rate per person-year, mean (range)	**3.7 (0–37)**
By AHP type	
AIP (N=104)	3.9 (0-37)
VP / HCP (N=8)	1.5 (0-4)
By region	
US (N=49)	3.3 (0–16)
Europe (N=63)	4.1 (0–37)
By patient-reported hemin prophylaxis at baseline	
Yes (N=52)	3.5 (0–20)
No/Unknown (N=60)	3.9 (0–37)
By patient-reported daily symptom status	
Yes (N=52)	3.4 (0–22)
No (N=57)	4.1 (0–37)

Data as of 21 Nov 2017

EXPLORE Natural History Study
Attack Risk Factors



- 9 factors analyzed for impact on risk for acute porphyria attacks in AHP patients
- AIP diagnosis, ≥3 attacks in prior 12 months, and hemin use for attacks with larger risk ratios

Data as of 21 Nov 2017
†Requiring hospitalization or hemin use. *Patient-reported at study entry

EXPLORE Natural History Study
Attack Treatment on Study

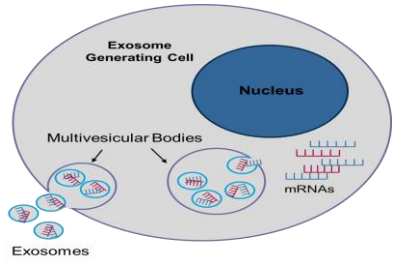
	US	Europe	Total
Total attacks, N	176	307	483
Attack treatment			
Treatment location, N (%)			
Home	48 (27)	100 (33)	148 (31)
Healthcare facility	127 (72)	207 (67)	334 (69)
Unknown	1 (0.6)	0 (0)	1 (0.2)
Treatment type, N (%)			
Included hemin	125 (71)	207 (67)	332 (69)
Included narcotics	86 (49)	175 (57)	261 (54)
Included carbohydrates, NSAIDs*, or other	80 (46)	137 (45)	217 (45)

Data as of 21 Nov 2017
*Non-steroidal Anti-inflammatory drugs.

EXPLORE Natural History Study
Disease Biomarkers on Study

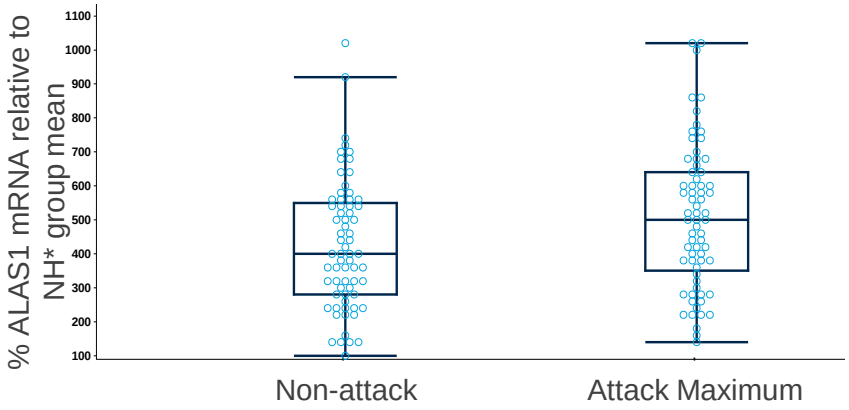
ALAS1 expression significantly elevated relative to normal and increases further during attacks

Liver ALAS1 mRNA via Circulating Extracellular RNA Detection (cERD)[1]



- Exosomes shed into bloodstream from various cells contain mRNA from different organs
- Correlation of liver and serum ALAS1 mRNA in preclinical studies[1]
- Exosomes may enable monitoring of porphyria activity via ALAS1 mRNA levels in urine or serum

ALAS1 mRNA by Urine cERD



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

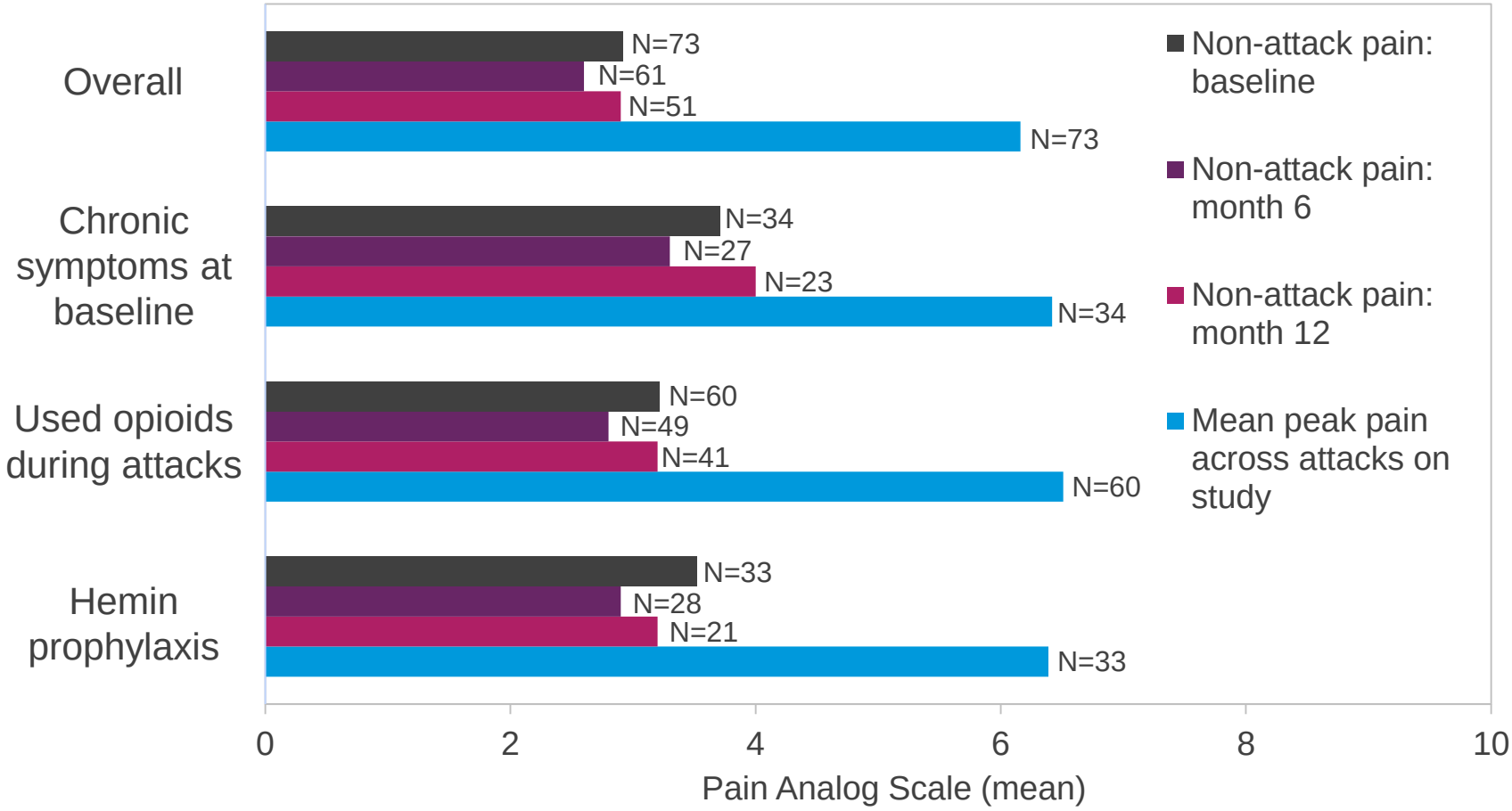
Urinary ALA and PBG significantly elevated relative to normal and increases further during attacks

Biomarkers	Upper Limit of Normal	Non-Attack Mean (range)	Attack Maximum Mean (range)
ALA (mmol/mol Cr)	<3.1	27.1 (1.0-211.0)	51.2 (1.0-1020.0)
PBG (mmol/mol Cr)	<1.2	27.3 (0.0-158.0)	55.5 (0.0-858.0)

Data as of 21 Nov 2017. Baseline ALAS1 mRNA for AIP patients was 4.7 versus non-AIP patients was 2.0.

1. Chan A, et al. Mol Ther—Nuc Acids. 2015;4:1-9. ALA; δ- Aminolevulinic acid. PBG; Porphobilinogen. ALAS1; ALA Synthase 1. Cr; creatinine.

EXPLORE Natural History Study
Pain Characteristics on Study



- Patients had chronic pain (3.5/10) in between attacks that increased during attacks (6.4/10)
- Non-attack pain persists at month 6 and month 12 regardless of porphyria treatment (hemin prophylaxis and opioids)

Data as of 21 Nov 2017.

EXPLORE Natural History Summary

Baseline Characteristics

- Significant proportion of patients had associated medical conditions, most commonly:
  - Nervous system (31%), psychiatric/sleep (30%), vascular (27%), gastrointestinal (22%), and renal (13%) disorders
- Mean of 9.3 attacks in prior 12 months, with 32% reporting >10 attacks in 12 months
- 65% of patients report chronic symptoms, most commonly pain, tiredness, anxiety and nausea, with 46% reporting daily symptoms
- Quality of life most negatively impacted in domains of usual activities, pain and anxiety/depression

On Study Results

- Patients had induced ALAS1 mRNA and high ALA and PBG compared to normal healthy individuals, that increase further during attacks
- Annualized attack rate (AAR) was 3.7 with mean attack duration of 7.3 days
  - AAR similar in groups reporting hemin prophylaxis at baseline or not (3.5 vs. 3.9, respectively)
- The factors with the larger risk ratio for attacks were:
  - AIP diagnosis, ≥3 attacks in prior 12 months, and hemin use for attacks
- Majority of attacks treated in healthcare facilities (69%), and included use of hemin (69%) and narcotics (55%)
- Patients reported chronic pain between attacks that increased during attacks, regardless of opioid or hemin prophylaxis treatment

EXPLORE results highlight unmet need for new therapeutic options to prevent attacks and ameliorate chronic symptoms

Please see posters SAT-040 and SAT-041 for further information on health care utilization and qualitative research on AHPs from the patient perspective

Data as of 21 Nov 2017. δ- Aminolevulinic acid. PBG; Porphobilinogen. ALAS1; ALA Synthase 1.

Acknowledgements

EXPLORE Investigators and Contributors

- Karl Anderson
- Herb Bonkovsky
- Montgomery Bissell
- John Phillips
- Charles Parker
- Manisha Balwani
- Joseph Bloomer
- Pauline Harper
- Eliane Sardh
- David Rees
- Mike Badminton
- Penny Stein
- Raili Kauppinen
- Jerzy Windyga
- Ulrich Stölzel
- Jorge Frank
- Elisabeth Minder
- Jean Charles Deybach
- Laurent Gouya
- Neila Talbi
- Pavel Martasek
- Janneke Langendonk
- Sverre Sandberg
- Felix Alegre
- Aneta Ivanova
- Paolo Ventura
- Maria Cappellini
- Joanne Marsden

APF

- Desiree Lyon
- Jessica Hungate
- Natalia Sturza

Mount Sinai

- Hetanshi Naik

Most importantly, we thank the patients for participating

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