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

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### Acute Hepatic Porphyria (AHP)

**Disease Overview**
- 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 Comorbidities**
- 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

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**Diagram of AHP Pathophysiology**

![Diagram of AHP Pathophysiology](image)

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**Table: AHP Disease Subtypes**

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Intermediates</th>
<th>AHP Disease Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALA Synthase (ALAS1)</td>
<td>Glycine + Succinyl CoA</td>
<td>ALA dehydratase-deficient porphyria (ADP)</td>
</tr>
<tr>
<td>ALA dehydratase</td>
<td>Aminolevulinic acid (ALA)</td>
<td>Acute intermittent porphyria (AIP)</td>
</tr>
<tr>
<td>Hydroxymethylbilane synthase</td>
<td>Porphobilinogen (PBG)</td>
<td></td>
</tr>
<tr>
<td>Uroporphyrinogen cosynthase</td>
<td>Hydroxymethylbilane</td>
<td></td>
</tr>
<tr>
<td>Uroporphyrinogen decarboxylase</td>
<td>Uroporphyrinogen</td>
<td></td>
</tr>
<tr>
<td>Coproporphyrinogen oxidase</td>
<td>Coproporphyrinogen</td>
<td></td>
</tr>
<tr>
<td>Protoporphyrinogen oxidase</td>
<td>Protoporphyrinogen</td>
<td></td>
</tr>
<tr>
<td>Ferrochelatase</td>
<td>Protoporphyrin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fe²⁺</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heme</td>
<td></td>
</tr>
</tbody>
</table>

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**Notes:**
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 coproporphyria (HCP) and variegate porphyria (VP)
- Recurrent attacks
  - ≥ 3 attacks\(^\text{a}\) 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
- Eligibility criteria expanded to ≥ 1 attacks\(^\text{a}\) within 12 months of screening
- Phone call every 3-6 months for 3 years; no clinic visits required

Part A Assessments
- Screening Clinic Visit
  - Questionnaires
  - Physical Examination
  - Blood and Urine Samples
- Month 2 and 4 Phone Call
  - Questionnaires
  - Mailed Urine Samples
- Every 6 Month Clinic Visit
  - Questionnaires
  - Physical Examination
  - Blood and Urine Samples

\(^\text{a}\)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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EU (n=63)</th>
<th>US (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>41 (13)</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>55 (87)</td>
<td>45 (92)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>52 (83)</td>
<td>43 (88)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>0</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Not answered</td>
<td>11 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166</td>
<td>165</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>AHP subtype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>61 (97)</td>
<td>43 (88)</td>
</tr>
<tr>
<td>Variegate porphyria</td>
<td>2 (3)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Hereditary coproporphyria</td>
<td>0</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

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”

\[ (n=112) \]

(reported by ≥50% of patients)

- Abdominal pain
- Arm/leg pain
- Back pain
- Muscle pain
- Headache
- Tiredness
- Trouble sleeping
- Anxiety
- Trouble concentrating
- Nausea
- Constipation
- Loss of appetite
- Vomiting
- Changes in urine color
- Weakness
- Fast heart beat
- Sweating

- Pain symptom
- Mood or sleep symptom
- Gastrointestinal symptom
- Other symptom

Patient (%)

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
Chronic symptoms are those occurring during asymptomatic periods

- 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 daily symptoms
- Similar to porphyria attacks, most common chronic symptom was pain

Patient-reported Chronic Symptoms at Baseline

<table>
<thead>
<tr>
<th>Symptom Category</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pain symptom</td>
<td>63.0</td>
</tr>
<tr>
<td>Any mood/sleep symptom</td>
<td>43.8</td>
</tr>
<tr>
<td>Any GI symptom</td>
<td>35.6</td>
</tr>
</tbody>
</table>

Most common (≥10%) chronic symptoms:

- Abdominal pain: 20.5%
- Other pain: 15.1%
- Anxiety: 19.2%
- Tiredness: 19.2%
- Nausea: 19.2%

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
On-Study Symptoms During Attacks

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

<table>
<thead>
<tr>
<th>Symptom Type</th>
<th>EU</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pain symptom</td>
<td>97.5</td>
<td>100</td>
</tr>
<tr>
<td>Any mood/sleep symptom</td>
<td>92.5</td>
<td>95.8</td>
</tr>
<tr>
<td>Any GI symptom</td>
<td>92.5</td>
<td>100</td>
</tr>
<tr>
<td>Any other symptom</td>
<td>87.5</td>
<td>92.5</td>
</tr>
</tbody>
</table>

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.
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

Commonly (>70%) Reported Symptoms During Attacks

<table>
<thead>
<tr>
<th>Symptom</th>
<th>EU (%)</th>
<th>US (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>77.5</td>
<td>91.7</td>
</tr>
<tr>
<td>Back pain</td>
<td>65.0</td>
<td>83.3</td>
</tr>
<tr>
<td>Arm/leg pain</td>
<td>65.0</td>
<td>70.8</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>75.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Tiredness</td>
<td>75.0</td>
<td>87.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>65.0</td>
<td>87.5</td>
</tr>
</tbody>
</table>

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)
Thank you to the patients and their families who contributed to this study and to the Patient Organizations for their support.

**Funding:** This study is sponsored by Alnylam Pharmaceuticals.