# **EXPLORE Part B: A Prospective, International, Long-term Natural History** Study of Patients with Acute Hepatic Porphyria with Recurrent Symptoms

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• For patients with AHP and recurrent attacks, including patients with relatively few attacks, the burden of disease is high, as evidenced by their having chronic symptoms between attacks and impaired QoL.

- · Acute hepatic porphyria (AHP) is a family of four rare genetic diseases caused by deficiency of enzymes that regulate hepatic heme biosynthesis 1-3
- Acute intermittent porphyria is the most common type; the other types are variegate porphyria hereditary coproporphyria, and delta-aminolevulinic acid (ALA) dehydratase-deficiency
- Depletion of the hepatic-free heme pool leads to induction of ALA synthase 1, the
- The resulting accumulation of the toxic heme intermediates ALA and porphobilinogen is likely responsible for the disease manifestations<sup>4-6</sup>
- AHP is characterised by acute neurovisceral attacks, which may be recurrent and life-threatening, cause chronic neuropathy, and negatively affect quality of life (QoL)3,4,7,8
- Intravenous hemin is recommended for treatment of acute attacks and can be used prophylactically: acute side effects include headache and phlebitis, and chronic side effects include iron overload and venous thrombosis9,10
- Hormonal suppression with gonadotropin-releasing hormone (GnRH) analogues has shown variable efficacy as prophylaxis for recurrent premenstrual attacks<sup>11,12</sup>
- EXPLORE (NCT02240784) was a two-part prospective natural history study of patients with AHP who experienced recurrent attacks<sup>13</sup>
- Part A followed patients by telephone and clinic visits for up to 12 months
- Patients often had attacks that required hemin or other treatment at a health care facility<sup>13</sup> Chronic symptoms impaired daily functioning<sup>13</sup>
- Part B included eligible Part A patients as well as newly enrolled patients and provided long-term evaluation of pain intensity and changes in disease activity for up to 3 years
- · The objective of this analysis was to evaluate disease activity, pain, and impact of symptoms on Ool in patients enrolled in EXPLORE Part B

- Patients with AHP who were ≥12 years old and eligible for Part B enrolment were required to provide written informed consent and meet one of these criteria:
- ≥1 attack that required increased pain medication, antiemetic, or carbohydrate intake, or hemin administration or hospitalisation for symptoms and signs of AHP (eg. severe abdominal pain. vomiting, tachycardia, constipation, hypertension, hyponatraemia), within the previous
- Hemin prophylaxis an average of ≥1 time per month within the 12 months before baseline

- Part B assessments were conducted by mail and confirmed by telephone every 3-6 months over
- . Changes in porphyria symptoms, potential precipitants of attacks, medical history, and medications taken were captured on a porphyria follow-up questionnaire
- Pain intensity and impact were measured with the Brief Pain Inventory-Short Form (BPI-SF), a 0-10 scale with higher scores indicating worse pain
- · QoL was evaluated with the EuroQol visual analog scale (EQ-VAS) and the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30),<sup>14</sup> both of which are 0–100 scales with higher scores indicating better

## Statistical Analysis

- · Results were analysed using descriptive statistics
- Data were analysed for all Part B enrollees; subgroup analyses were performed to assess findings in patients with ≥3 attacks or prophylaxis and patients with <3 attacks without prophylaxis</li>

- In total, 136 patients from 18 countries (including 43 Part A patients) were enrolled in Part B
- Table 1 summarises patients' baseline demographic and disease characteristics
- Most patients were female (90%) and white (85%) and had acute intermittent porphyria (90%).

## Table 1. Baseline Demographic and Disease Characteristics of Patients With AHP Enrolled in EXPLORE Part B

Characteristic	Total Population (N=136)
Age at time of consent, y	
Mean (SD)	41.0 (12.6)
Median (range)	40.0 (17-83)
Female, n (%)	123 (90.4)
Race, n (%)	
White	115 (84.6)
Asian	9 (6.6)
Black/African American	6 (4.4)
Other	5 (3.7)
Not stated	1 (0.7)
Geographic region, n (%)	
Europe	70 (51.5)
North America	56 (41.2)
Other (Africa, Asia, Australia)	10 (7.4)
Years since AHP diagnosis <sup>a</sup>	
Mean (SD)	11.3 (11.7)
Median (range)	6.3 (0.0-45.7)
AHP etiology, n (%)	
Acute intermittent porphyria	123 (90.4)
Variegate porphyria	11 (8.1)
Hereditary coproporphyria	2 (1.5)
Months on study	
Mean (SD)	17.7 (11.0)
Median (range)	14.6 (2.0-41.5)
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## Disease History

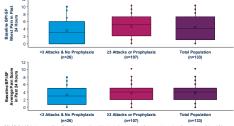
- Within the 12 months before enrolment, all patients had a median (range) of 3 (0–52) acute attacks; 46% were receiving hemin and/or GnRH prophylaxis (Table 2)
- . The subgroup of 26 patients with <3 attacks a year without prophylaxis had a median (range) of 1 (0–2) acute attacks within the 12 months before enrolment, with pain being the most commor symptom (Table 2)
- During attacks, most patients required bemin (69%) and pain medication (96%) including
- Most patients (85%) also had chronic symptoms

## Table 2. History of Attacks, Prophylaxis, and Chronic Symptoms in Patients with AHP

Characteristic	<3 Attacks/Year without Prophylaxis (n=26)	≥3 Attacks/Year or Prophylaxis (n=110)	Total Population (N=136)
Number of attacks within previous 12 mo, median (range)	1.0 (0-2)	4.0 (0-52)	3.0 (0-52)
Prophylaxis within previous 12 mo, n (%)	0	62 (56.4) <sup>b</sup>	62 (45.6) <sup>b</sup>
Hemin	0	56 (50.9)b	56 (41.2) <sup>b</sup>
GnRH	0	17 (15.5)	17 (12.5)
Symptoms associated with attacks within previous 12 mo, n (%)c			
Pain	26 (100.0)	97 (88.2)	123 (90.4)
Mood/sleep	25 (96.2)	92 (83.6)	117 (86.0)
Digestive/bladder	23 (88.5)	95 (86.4)	118 (86.8)
Nervous system	22 (84.6)	89 (80.9)	111 (81.6)
Other	19 (73.1)	87 (79.1)	106 (77.9)
Patients reporting chronic symptoms within previous 12 mo, n (%)	22 (84.6)	79 (71.8) <sup>b</sup>	101 (74.3) <sup>b</sup>

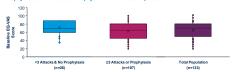
- In patients with <3 attacks without prophylaxis at baseline, mean worst pain and average pain</li> scores on the BPI-SF were 3.5 and 3.3, respectively (Figure 1)
- Among those taking pain medications regularly (n=18), patients on average reported having
- In patients with ≥3 attacks or prophylaxis at baseline, mean worst pain and average pain scores on the BPI-SF were 4.5 and 3.7, respectively (Figure 1)

## Figure 1. Pain Intensity at Baseline as Assessed With BPI-SF Scores for Subgroups of Patients With <3 Attacks Without Prophylaxis or ≥3 Attacks or Prophylaxis and for



. Mean EQ-VAS score was 71.8 in the subgroup with <3 attacks without prophylaxis and 62.9 in the subgroup with ≥3 attacks or prophylaxis (Figure 2)

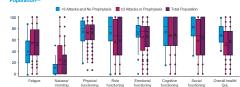
Figure 2. Mean EQ-VAS Scores at Baseline for Subgroups of Patients with <3 Attacks without Prophylaxis or ≥3 Attacks or Prophylaxis and for Total Population<sup>a,b</sup>



\*\*Data shown are for patients with available data. \*\*On the EQ-VAS, a standard vertical 20-cm visual analog scale, individuals self-rate their current overall health-related QoL from 0 ("the worst imaginable health state"). \*\*I

. Mean EORTC QLQ-C30 overall health/QoL scores were 68 and 54, respectively (Figure 3)

## Figure 3, Mean FORTC OL O.C30 Total and Subscale Scores at Reseline for Subgroups of



- · Number of attacks was self-reported by patients and was not verified by a clinician or confirmed with testing of ALA and porphobilinogen levels
- Patients may have had symptoms similar to those of attack symptoms but unrelated to AHP, resulting in overestimates of number of attacks

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