# Management of Recurrent Acute Hepatic Porphyria (AHP) Attacks in Europe and the United States: EXPLORE International, Prospective, Natural History Study

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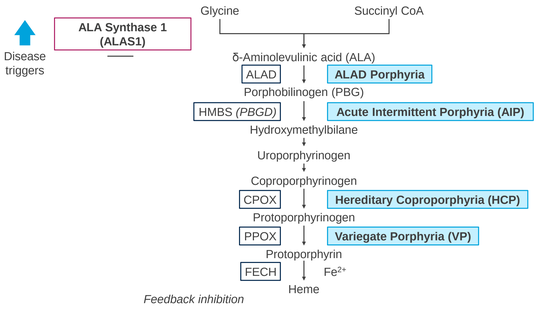
## Introduction

- Acute hepatic porphyria (AHP) is a family of rare genetic diseases caused by enzyme deficiencies involved in heme biosynthesis in the liver,[1,2] leading to accumulation of neurotoxic heme intermediates[3–5] (Figure 1)
- Clinical manifestations comprise life-threatening acute attacks including abdominal pain, acute polyneuropathy and mental symptoms. Around 3–8% of patients have recurrent attacks,[3, 5–7] resulting in chronic neuropathy and encephalopathy. Long-term complications such as renal failure, hypertension, and hepatoma may occur[8–10]

### Figure 1: AHP Enzymatic Pathway




- The only approved treatment for acute attack symptoms is hemin[11,12]
- Recurrent attack prevention strategies include trigger avoidance, hormonal interventions, and off-label hemin prophylaxis,[3,13] and liver transplantation[14]
- EXPLORE was designed to characterize the natural history and current clinical management of patients with AHP with recurrent attacks
  - Given healthcare system differences between the regions, this analysis aimed to characterize AHP recurrent attack management in the EU and the US

## Methods

- EXPLORE (NCT02240784) is a prospective, multinational, observational study to characterize the natural history and clinical management of symptomatic patients with AHP (Figure 2)

### Figure 2: EXPLORE Study Design


^Attacks defined as typical symptoms requiring increase in treatment (hemin, pain medications, or carbohydrates) or hospitalization

- Male or female patients (≥18 years) with a diagnosis of AHP who had experienced ≥3 attacks within 12 months prior to the baseline visit or were receiving prophylaxis to prevent attacks were included
- On separate questionnaires, investigators and patients reported attack history, including hemin use for attacks and off-label prophylaxis
- Descriptive statistics were used to analyze outcomes, treatment location, and dosing frequency/duration by region

## Results*

### Patient Demographics and Disposition

- A total of 112 patients were enrolled from 13 countries, including 14 EU centers and 7 US centers (Table 1)
  - European countries included Bulgaria, Czech Republic, England, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Switzerland, and Wales
- 107 (96%) and 80 (71%) patients completed 6 and 12 months of follow-up, respectively

### Table 1: Patient Demographics and Characteristics

| Characteristic | EU (n=63) | US (n=49) | All patients (N=112) |
|---|---|---|---|
| Age in years, mean (SD) | 41.2 (13.3) | 36.9 (11.8) | 39.3 (12.8) |
| Female sex, n (%) | 55 (87) | 45 (92) | 100 (89) |
| Ethnicity, n (%) | | | |
| White/Caucasian | 52 (83) | 43 (88) | 95 (85) |
| Asian | 0 (0) | 3 (6) | 3 (3) |
| Black/African American | 0 (0) | 3 (6) | 3 (3) |
| Not answered | 11 (18) | 0 (0) | 11 (10) |
| AHP type, n (%) | | | |
| AIP | 61 (97) | 43 (88) | 104 (93) |
| HCP | 0 (0) | 3 (6) | 3 (3) |
| VP | 2 (3) | 3 (6) | 5 (5) |
| Time (years) since first attack, mean (SD) | 11.9 (8.8) | 10.4 (10.2) | 11.3 (9.4) |

AHP, acute hepatic porphyria; AIP, Acute intermittent porphyria; HP, hereditary coproporphyria; SD, standard deviation; V, variegate porphyria

### Attacks Prior to EXPLORE

- In the 12 months preceding the study, patients experienced a mean of 9 attacks, one third of which required hospitalization (Table 2)
- There was a wide range of attack frequency among patients (range = 0–52)

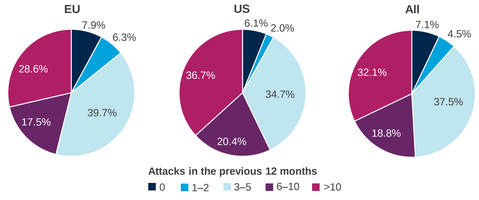
### Table 2: Attack Rate in the Last 12 months Before EXPLORE

| Number of Attacks | EU (n=63) Mean (SD) | US (n=49) Mean (SD) | All patients (N=112) Mean (SD) |
|---|---|---|---|
| Total | 9.0 (10.6) | 9.7 (9.2) | 9.3 (10.0) |
| Requiring hospitalization | 3.2 (3.9) | 3.5 (4.1) | 3.3 (4.0) |
| Requiring treatment at outpatient clinic or infusion center | 3.9 (8.2) | 3.7 (7.0) | 3.8 (7.6) |
| Requiring treatment at home | 3.3 (8.6) | 3.0 (5.7) | 3.2 (7.4) |

SD, standard deviation

- Over 90% of patients experienced attacks in the previous 12 months (Figure 3)
  - A range of 3–5 attacks or >10 attacks were the most commonly reported

### Figure 3 Number of Attacks in the Last 12 months Before EXPLORE




### Prophylactic Use to Prevent Attacks

- Sixty-two patients reported use of any prophylaxis at baseline, 52 of whom reported prophylactic hemin use, mostly weekly (Table 3)
- Prophylactic treatment appeared to be less common in the EU (43%) than in the US (71%)

### Table 3: Baseline Prophylactic Medications

| Characteristic | EU (n=63) | US (n=49) |
|---|---|---|
| Any prophylaxis, n (%) | 27 (43) | 35 (71) |
| Hemin | 26 (41) | 26 (53) |
| When anticipating attack | 5 (8) | 6 (12) |
| On a regular basis | 25 (40) | 24 (49) |
| Weekly | 13 (21) | 12 (24) |
| Monthly | 4 (6) | 5 (10) |
| Other | 8 (13) | 7 (14) |
| Unknown | 1 (2) | 0 |
| GnRH analog | 2 (3) | 5 (10) |
| Other | 5 (8) | 20 (41) |
| No prophylaxis used/unknown | 36 (57) | 14 (29) |
| Time in years on hemin prophylaxis, mean (SD) | 9.9 (7.7) | 4.3 (4.5) |
| Time in years on GnRH prophylaxis, mean (SD) | 0.4 (0.05) | 0.9 (1.2) |

GnRH, gonadotropin-releasing hormone; SD, standard deviation

- The attack rate for patients on hemin prophylaxis versus those who had never used hemin prophylaxis prior to screening was similar (Table 4)
- A greater proportion of patients who had used prior prophylactic hemin required treatment at an outpatient clinic or infusion center (Table 4)

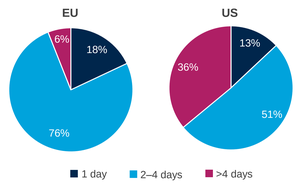
### Table 4: Mean Number of Attacks in the Last 12 Months in Patients Who Had or Had Never Used Hemin Prophylactically Prior to Screening

| Number of attacks Mean (SD) | Had used prophylactic hemin prior to screening | Never used prophylactic hemin prior to screening |
|---|---|---|
| Total | 10.0 (11.1) | 8.7 (8.9) |
| Requiring hospitalization | 3.0 (4.1) | 3.5 (3.9) |
| Requiring treatment at outpatient clinic or infusion center | 6.0 (9.7) | 2.0 (4.6) |
| Requiring treatment at home | 2.5 (6.6) | 3.7 (8.0) |

These data are skewed right due to some patients having very frequent attacks
SD, standard deviation

- The data show a trend towards a longer duration of hemin treatment for an attack in the US than in the EU (Figure 4)

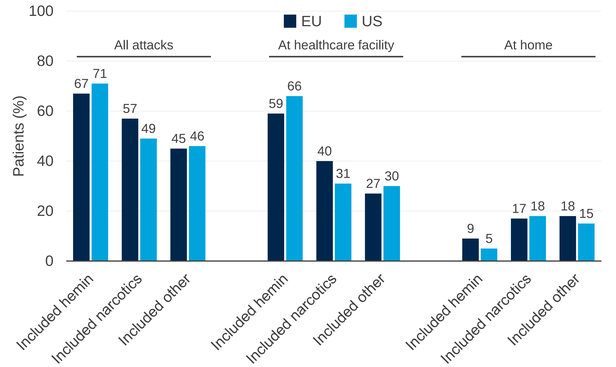
### Figure 4: Usual Frequency of Hemin Use Per Attack in the Last 12 Months Before EXPLORE




### Attacks During EXPLORE

- Overall, 98 (87.5%) patients experienced a total of 483 attacks on-study (EU: 176; US: 307), 69% of which required treatment at a healthcare facility
- The proportion of attacks treated at home or at healthcare facilities were similar in the EU and the US
- Attacks were treated with hemin (most common), narcotics, and other medications, mostly administered at a healthcare facility (Figure 5)

### Figure 5: Treatment of Attacks During EXPLORE




Other includes carbohydrates, non-opioid analgesics, and anxiolytics

## Conclusions

- Management of AHP was generally similar between the EU and the US
- At baseline, off-label hemin prophylaxis in patients with recurrent attacks (i.e. those chronically affected with severe AHP) appeared to be less and hemin treatment duration for attacks seemed to be shorter in the EU than in the US
  - Patient selection bias and variable access to treatments may account for this difference
- Attack rates were similar among patients who had and who hadn't received off-label prophylactic hemin
- Attack rates among patients with severe AHP with recurrent attacks were high, with a large proportion of patients requiring extensive treatment at healthcare facilities, underscoring the need for therapies to address AHP unmet medical needs in both the EU and US

## Acknowledgements & Disclosures

**Acknowledgements:** Thank you to the patients, investigators, and study staff who participated in these studies and the American Porphyria Foundation for support. Editorial assistance in the development of the poster was provided by Adelphi Communications Ltd, UK, funded by Alnylam Pharmaceuticals.

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

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*Data Transfer: November 21, 2017