Disease Characteristics of Patients with Acute Hepatic Porphyria Patients: ENVISION, a Phase 3 Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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Introduction

Acute Hepatic Porphyria (AHP)

- Family of rare, genetic diseases due to a defect in one of the enzymes of the heme biosynthesis pathway in the liver[1]
- Characterized by potentially life-threatening attacks and, in some patients, chronic manifestations that negatively impact daily functioning and quality of life[2]
- AHP is also associated with multiple long-term complications, including chronic neuropathy,[3] hypertension,[3,4] iron overload, liver disease and chronic kidney disease[4]

Givosiran

- Givosiran, a subcutaneously administered investigational RNAi therapeutic in development for the treatment of AHP, specifically targets 5-aminolevulininic acid synthase 1, the first and rate-limiting enzyme of the heme biosynthesis pathway in liver, to reduce the accumulation of toxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), which are causal for disease manifestations in AHP[7,8]

Objectives

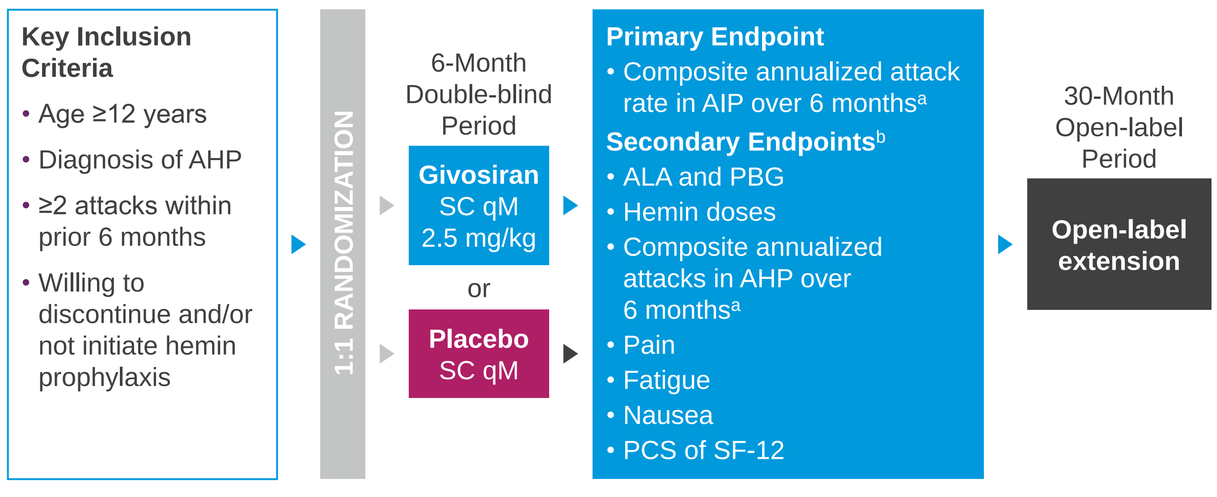
- Provide a detailed description of baseline disease characteristics of patients with AHP enrolled in the ENVISION Phase 3 global, multicenter, randomized, double-blind, placebo-controlled trial (**Figure 1**); please see Gouya and Sardh et al (ICPP, 2019) for efficacy and safety outcomes

Methods

ENVISION Phase 3 Study

- ENVISION (NCT03338816) was a Phase 3 global, multicenter, randomized, double-blind, placebo-controlled trial with an open label extension to evaluate the efficacy and safety of subcutaneous givosiran in AHP patients **(Figure 1)**. Detailed medical history and laboratory assessments were obtained at baseline
- Eligible patients were aged ≥12 years with an AHP diagnosis and ≥2 attacks (requiring hospitalization, urgent healthcare visit, or treatment with intravenous hemin at home) within prior 6 months, or were receiving hemin prophylaxis. Patients were required to discontinue and/or not initiate the use of prophylactic hemin at baseline and for the duration of the trial. Investigators managed attacks according to the local standard of care, which could include use of intravenous hemin

Figure 1. ENVISION Study Design



[†]Attacks requiring hospitalization, urgent healthcare visit, or at-home hemin administration
*Endpoints evaluated in genetically-confirmed AIP patients, unless otherwise noted

Of note, key exclusion criteria included the following laboratory parameter assessments at screening:

- Alanine aminotransferase >2× upper limit of normal (ULN)
- Total bilirubin (TBL)>1.5× ULN. Patients with elevated TBL secondary to documented Gilbert's syndrome were eligible if the TBL was <2× ULN
- International normalized ratio (INR) >1.5 (patients on an anticoagulant [e.g., warfarin] with an INR <3.5 was allowed)
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 using the Modification of Diet in Renal Disease formula
- Known active HIV infection or evidence of current or chronic hepatitis C virus or hepatitis B virus infection

Results

Baseline Demographics

- ENVISION enrolled 94 patients with AHP, with a mean (range) age of 37.5 (19–65) years
- A total of 109 patients were screened, with 15 patients (14%) not meeting eligibility criteria
  – 3 of 15 patients failed screening due to elevated liver enzymes levels (>2x ULN)
- Baseline demographics and the disease characteristics of patients of the overall AHP ENVISION population are shown in (**Table 1)**
- Overall, 89.4% of patients were female, with a median (range) of 6.5 (0.1–43) years since diagnosis. Patients had a median historical annualized attack rate of 8 and 40.4% were on hemin prophylaxis prior to study (**Table 1**)
- 52.1% of patients experienced daily chronic symptoms and 28.7% used opioids daily/most days between attacks (**Table 1**)

Table 1. Baseline Demographics and Characteristics of Patients of the Overall AHP ENVISION Population

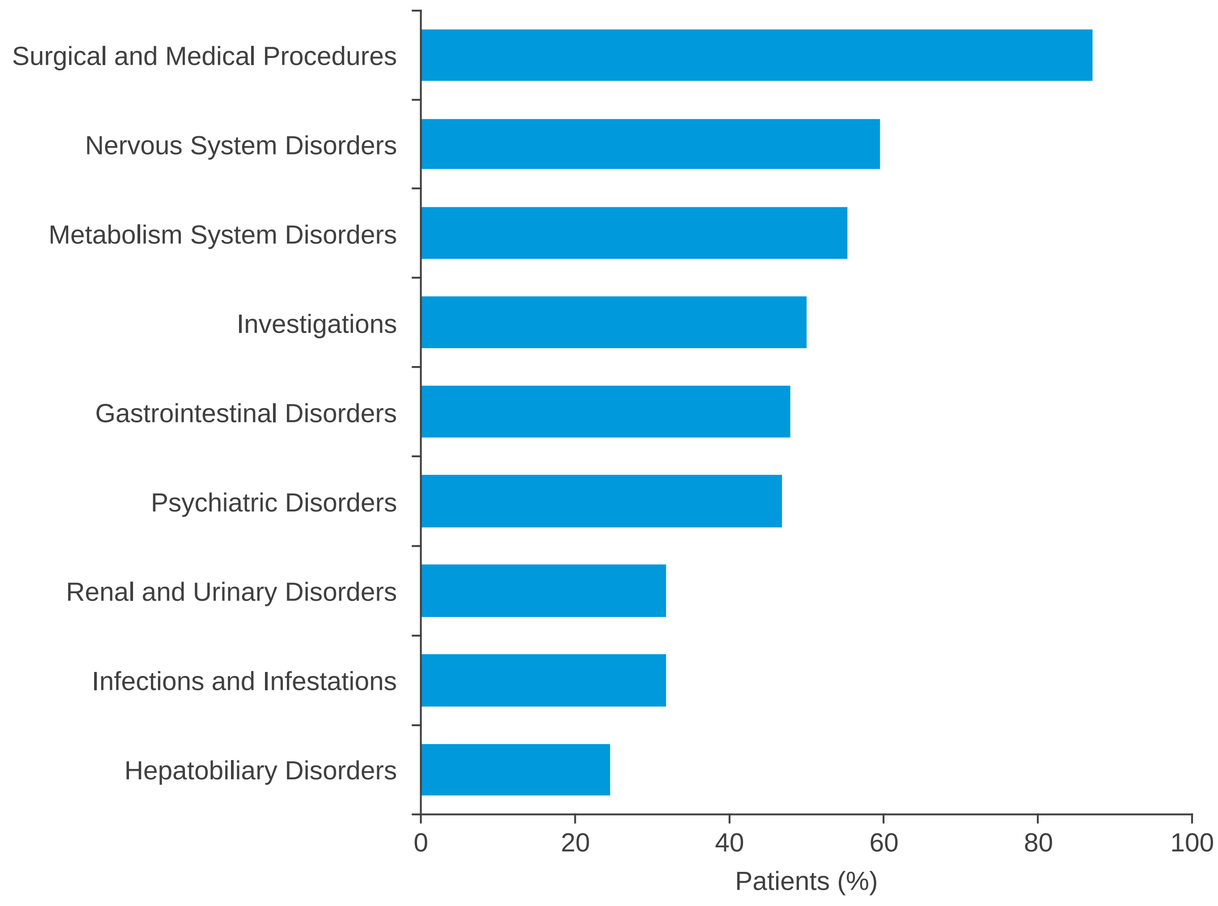
Demographics/Characteristics	US (N=94)
Mean (SD) age, years	38.8 (11.4)
Female, n (%)	84 (89.4)
Mean (SD) time since diagnosis, years	9.7 (10.0)
Median (range) number of attacks 6 months prior to screening	3 (0–25)
Prior hemin prophylaxis, n (%)	38 (40.4)
Prior chronic symptoms, n (%)[a]	49 (52.1)
Prior chronic opioid use, n (%)[b]	27 (28.7)
Median (range) historical AAR[c]	8 (0–46)

[a]Patients experienced symptoms of porphyria when not having an attack daily or on most days prior to the study
[b]Patients taking opioids for porphyria when not having an attack daily or on most days
[c]Historical AAR was calculated based on the number of attacks requiring hospitalization, healthcare facility visit or hemin use at home during the 6 months prior to randomization

Results (continued)

- At baseline, 24.5% of patients in the overall AHP population had medical history terms within the Hepatobiliary Disorders System Organ Class, 67.2% within Surgical and Medical Procedures, 59.6% within Nervous System Disorders, 55.3% within Metabolism and Nutrition Disorders, 50.0% with in Investigations, 47.9% within Gastrointestinal Disorders, and 46.8% within Psychiatric Disorders (**Figure 2**)

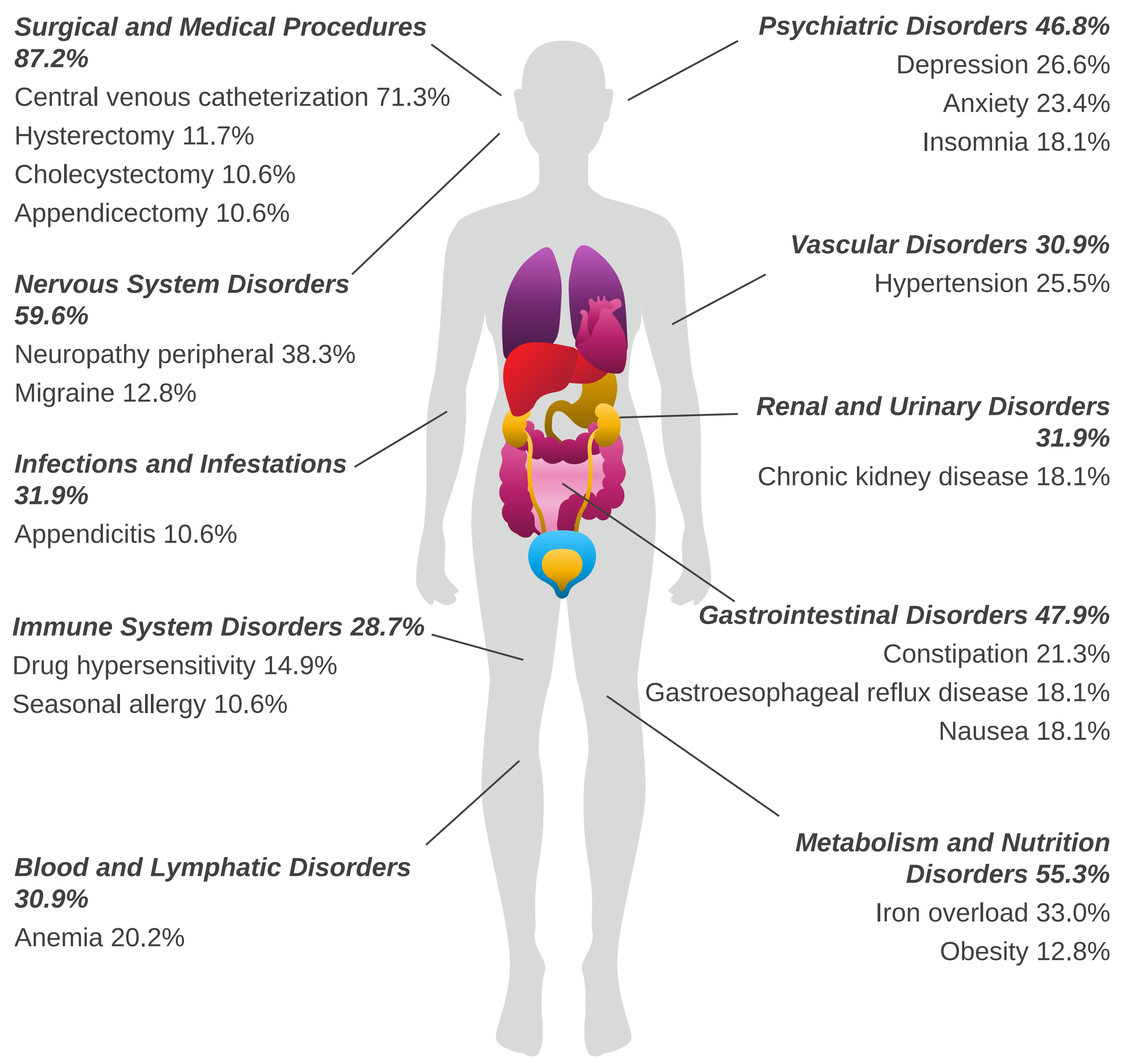
Figure 2. Select Medical History in the Overall AHP ENVISION Population by System Organ Class[a]



[A]>30% plus Hepatobiliary disorders, Excluding AHP (Congenital, Familial, and Genetic Disorders system organ class)

- Medical history by preferred terms in the overall AHP population included peripheral neuropathy (38.3%), iron overload (33.0%), liver disease (27.7%), depression (26.6%), hypertension (25.5%), anxiety (23.4%), anemia (20.2%), insomnia (18.1%), gastroesophageal reflux disease (18.1%), nausea (18.1%, and chronic kidney disease (18.1%) (**Figure 3**).
- Multiple comorbidities and complications were often overlapping in the same patients

Figure 3. Medical History in the Overall AHP ENVISION Population by Preferred Term in ≥10% of Patients



Key Laboratory Abnormalities

- Results of liver function tests at baseline showed 37.2% of patients had increased liver transaminases
  – 12.8% of patients had elevated ALT concentrations and 12.8% had elevated AST concentrations
- Renal function tests showed 34.0% of patients had an eGFR <60 mL/min/1.73 m2 at baseline
- Mineral and electrolyte tests showed 3.2% of patients had elevated serum ferritin at baseline

Conclusions

- The baseline disease characteristics of the Phase 3 study population demonstrate the high burden of disease complications in these patients, across multiple organ systems
- ENVISION patient disease characteristics are representative of those reported in the AHP literature. These patients experience comorbidities at a higher prevalence than a general age-matched population, in particular with regards to surgical and medical procedures, psychiatric disorders, and chronic kidney disease[1]
- The results underscore the medical complexity of caring for patients with AHP and the potentially high degree of healthcare utilization for patients with the disease
- The multisystemic nature of AHP highlights the challenge and the urgency in treating this disease

Abbreviations: AAR, annualized attack rate; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALT, alanine aminotransferase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PBG, porphobilinogen; PCS, Physical Component Summary; qM, every month; SC, subcutaneous; RNAi, ribonucleic acid interference; SD, standard deviation; SF-12, Short-Form (12-item) Health Survey; SOC, System Organ Class; TBL, total bilirubin; ULN, upper limit of normal.

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QR Placeholder